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Patents ADP number *(if you know it)*		7652134001
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom	
4. Title of the invention	Compound	
5. Name of your agent *(if you have one)*	D Young & Co	
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	21 New Fetter Lane London EC4A 1DA	
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11. I/We request the grant of a patent on the basis of this application.

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D Young & Co (Agents for the Applicants)

Date 17 October 2001

12. Name and daytime telephone number of person to contact in the United Kingdom — David Alcock — 023 8071 9500

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COMPOUND

Breast cancer is a devastating disease which remains to be a major cause of death for women in most Western countries. It is estimated to affect approximately 1 million women per year across the globe.[1]

Britain has one of the highest mortality rate for breast cancer in the world with over 35 000 women diagnosed each year accounting for nearly one in five of all cancer cases. It is estimated that 1 in 10 women living to the age of 85 in Britain will develop breast cancer during the course of her life. Although modern methods of treatment as well as an earlier detection of the disease have greatly improved survival rates, breast cancer remains the leading cause of death for women aged between 35-54.[2]

All women are at risk of breast cancer although a number of risk factors have been identified, most of them being related to women's hormonal and reproductive history as well as their family background of the disease. Women at higher risk are generally those with a strong family history of the disease, early onset of menarche, late onset of menopause or a first full-term pregnancy after the age of 30.[2]

In the earliest stages of a breast cancer, surgery appears to be the treatment of choice. In most of the cases, breast conserving surgical techniques, such as local incision of lump(s) in the breast(s), are involved rather than mastectomy. To prevent any recurrence of the disease, radiotherapy is often prescribed, particularly if breast conserving techniques have been involved.[3] It is also used to reduce large tumours to an operable size so that conservational surgery can be carried out.[4]

For advanced breast cancers, when the tumour has spread or recurred, the aim in the treatment is no longer to cure but to reach a palliative control. This is the case when metastases of the tumour have reached locations such as bones, skin, lymph, node or brain. The treatment varies depending on the hormonal status of the patient (whether it is a pre- or post-menopausal woman to be treated) and depending on the type of tumour. Certain tumours have indeed been proven to rely on estrogens for their growth and development, leading to what is called a Hormone Dependent Breast Cancer (HDBC, see I-1). While non HDBC are treated with chemotherapy, where the aim is to kill differentially tumour cells using a combination of cytotoxic agents,[5] HDBC are expected

to respond to endocrine therapy.

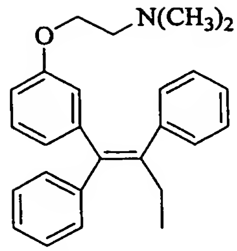
I – 1 – Hormone Dependent Breast Cancer and endocrine therapy

The concept of hormone dependent tumours appeared in the early 1960s, when the model of estrogens action was first introduced.[6] In order for estrogens to regulate cell growth and function in humans, a specific protein, called the human Estrogen Receptor (hER), must be present.[7] This protein, localized in the nucleus, interacts with estrogens resulting in the formation of a binding complex. This acts as a transcription factor by activating production of *m*-RNA from specific genes, one or more of which are probably essential for efficient tumour cell growth.

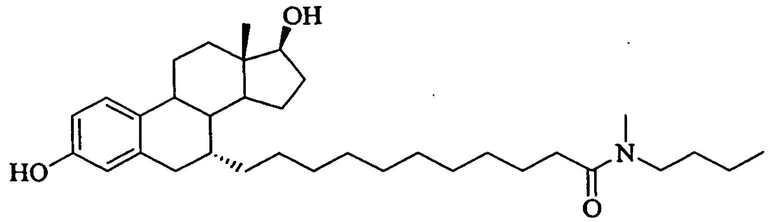
Patients with a measurable level of receptor protein are classified as estrogen-receptor-positive (ER+) with opposition to estrogen-receptor-negative (ER-). About 50% of pre-menopausal women and 75% of post-menopausal women fall into the ER+ group[8] where the development of breast cancers can be directly linked to the presence of estrogens. Endocrine therapy, where the use of drugs results in a deprivation of estrogenic stimulation to cells, has proven to be an effective approach to the treatment of HDBC. Originally, two classes of drugs, responding to different strategies, were developed: antiestrogens and aromatase inhibitors.

Antiestrogens, as antagonists of the estrogen receptor, have been one of the first treatment considered for HDBC. Their action rey on their ability to bind competitively to the specific receptor protein hER, thus preventing access of endogenous estrogens to their specific binding site. Consequently, the natural hormone is unable to maintain tumour growth.

Of the antiestrogens commonly used in breast cancer therapy, tamoxifen (Figure 1) is the most widely used because of the very low toxicity profile of the molecule. Despite its non-steroidal skeleton, tamoxifen possesses a mixed agonist-antagonist activity that limits its therapeutic potential.[9] In addition, some form of drug resistance has been reported in patients after long-term tamoxifen treatment.[10]
Novel pure antiestrogenic drugs, such as ICI 164384 (Figure 1), have since been discovered but the loss of potency compared with that of tamoxifen suggested the need to design more highly potent targets.[11]



Tamoxifen



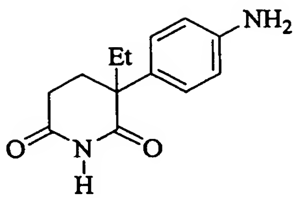
ICI 164384

Figure 1. Structure of estrogen antagonists: tamoxifen, and ICI 164384.

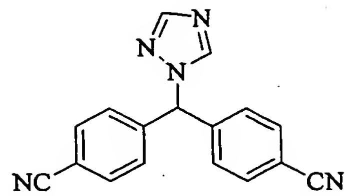
For some years now, a new type of antiestrogen has emerged, combining estrogen agonism on target tissues such as bone or liver and antagonism and/or minimal agonism in reproductive tissues such as breasts or uterus.[12] These compounds, designed as Selective Estrogen Receptor Modulators (SERMs), are not only potentially effective in reducing a patient's risk of breast carcinoma but they have also been shown to increase bone mineral density and prevent osteoporosis in post-menopausal women. Raloxifen is the first of this class of compounds to be used clinically.[13] More SERMs are currently in clinical trials and these molecules might one day replace tamoxifen as the first line treatment for women with HDBC.

The use of therapeutic agents that inhibit one or several enzyme of the steroid biosynthesis pathway represents another important strategy to control of the development of estrogen-dependent tumours.[14] The enzyme aromatase, which converts androgenic C19 steroids to estrogenic C18 steroids, has been the prime target for reducing estrogen levels. This enzyme complex, which contains a cytochrome P450 haemoprotein, catalyses the aromatisation of the androgen A-ring with the subsequent loss of the C19 methyl group to yield estrogens.

Aminoglutethimide (AG, Figure 2) was the first aromatase inhibitor used for the treatment of breast cancer. It however showed a number of undesirable side effects given its wide spectrum of inhibitory effects on other P450-dependant enzymes, and attempts to improve on the original structure have led to a number of non-steroidal compounds entering clinical trials.[15] The last generation developed compounds such as letrozole, which combine high potency and high selectivity for the enzyme, and are also better tolerated.



AG



Letrozole

Figure 2. Structure of different types of aromatase inhibitors.
Generation I : aminoglutethimide, AG; generation III, letrozole.

Traditionally, aromatase inhibitors are reserved as second line treatment for advanced HDBC patients whose diseases are no longer controlled by tamoxifen. However, because of the extreme good toxicity profile of some of the latest aromatase inhibitors, recent clinical trials have been conducted to assess their suitability as first line treatment for HDBC.

I – 2 – Latest targets for endocrine therapy

Strong evidence has emerged over the past decade, both biochemically and clinically, that the sole inhibition of the enzyme aromatase cannot afford an effective reduction of estrogenic stimulation to HDBC, the reason being that other pathways are involved in estrogen biosynthesis. The sulfatase pathway is now considered to be the major route for breast tumour estrogen synthesis since sulfatase activity was found to provide 10 fold more estrone than the aromatase activity.[16]

In the sulfatase pathway, estrogens are synthesized from the highly available precursor estrone-sulfate, *via* two enzymes (Figure 3): estrone sulfatase (STS) which hydrolyses estrone-sulfate into estrone, and 17β-hydroxysteroid dehydrogenase (17β-HSD) which reduces estrone into estradiol. These two enzymes represent the latest targets for estrogen deprivation strategies.

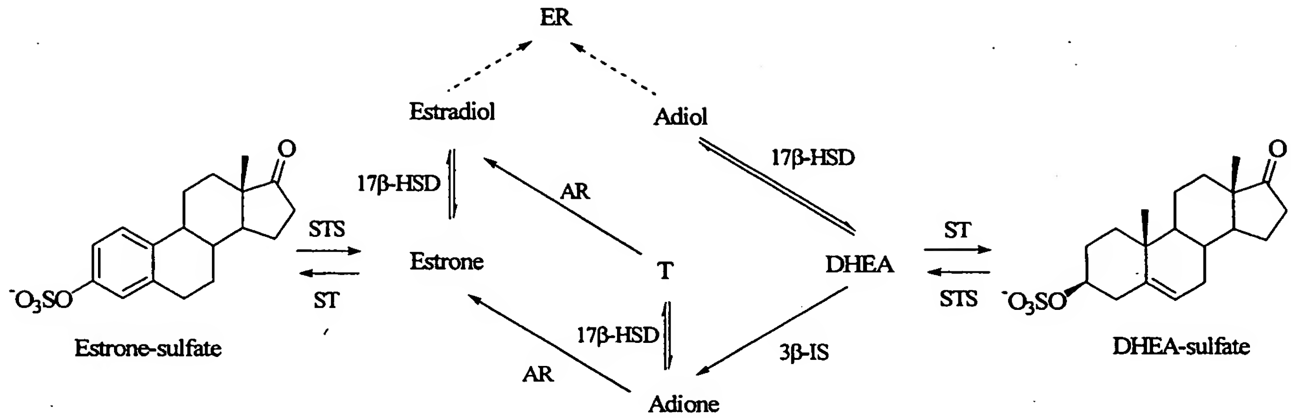
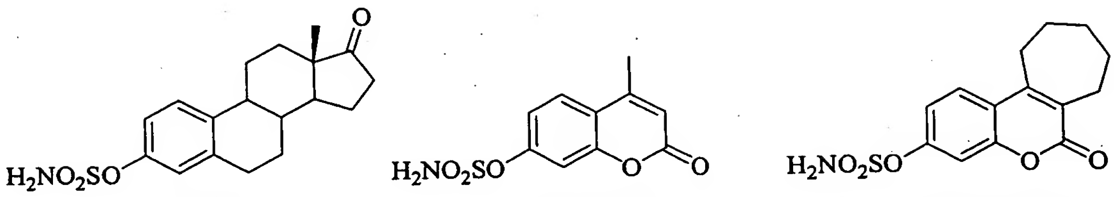


Figure 3. Origin of estrogens in normal and tumoral breast cells. AR, aromatase; ST: steroid sulfotransferase; STS, steroid sulfatase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; 3β-IS, 3β-hydroxysteroid dehydrogenase Δ^5,Δ^4-isomerase; ER, estrogen receptor.

Several potent inhibitors have been identified for estrone sulfatase. They all share the common structural feature of an aromatic ring bearing a substituent that mimics the phenolic A-ring of the enzyme substrate, estrone-sulfate. On the development of steroidal inhibitors, a wide variety of chemical groups have been introduced at C3, of which the 3-*O*-sulfamate was found to be the most potent for the estrone molecule. The resulting compound, estrone-3-*O*-sulfamate (EMATE, Figure 4) led to the identification of the aryl-O-sulfamate structure as an active pharmacophore required for potent inhibition of STS. EMATE was shown to inhibit steroid sulfatase activity in a time- and concentration-dependent manner[17] and was active in vivo on oral administration.[18] It was however revealed to be highly estrogenic which raised the need to design STS inhibitors devoid of agonist activity on hER.

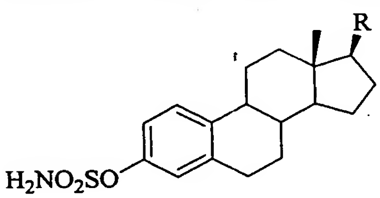
To avoid the problems linked to an active steroid nucleus, non steroid-based inhibitors have been synthesized. Coumarin sulfamates such as 4-methylcoumarin-7-*O*-sulfamate (COUMATE, figure 4), where the active pharmacophore is conserved, have been among the first inhibitors of that type to be identified.[19] Although COUMATE is less potent than EMATE, it has the advantage of being non estrogenic.[20] Some tricyclic coumarin-based sulfamates have also been developed and turned out to be much more potent than COUMATE, while retaining its non estrogenic characteristic.[21] 667COUMATE (Figure 4), which is some 3 times more potent than EMATE *in vitro* is now in pre-clinical development for clinical trials.[22]



EMATE COUMATE 667COUMATE

Figure 4. Structures of the steroid sulfatase inhibitors EMATE, COUMATE and 667COUMATE.

Molecules combining both features of STS inhibitors and antiestrogens have also been developed. Relying on the fact that an alkylamide side-chain can block the estrogen receptor activation,[23] 3-*O*-sulfamates derivatives of estradiol bearing 17β-(*N*-alkylcarbamoyl) and 17β-(*N*-alkanoyl) side-chains have been synthesised.[24] The alkyl/alkanoyl group is designed as membrane insertion region that should increase the affinity for the enzyme and decrease the estrogenicity of the steroid. These novel molecules represent potential therapeutic agent for treatment of HDBC since the activity of the heptyl analogues **1** and **2** (Figure 5) was found to be similar to that of EMATE with respect to the inhibition of estrone sulfatase, without being estrogenic.



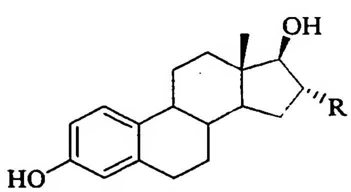
1 R = $NHCO(CH_2)_6CH_3$
2 R = $CONH(CH_2)_6CH_3$

Figure 5. Structures of 3-*O*-sulfamates-C17-derivatives of estrone bearing *N*-alkylcarbamoyl side-chains.

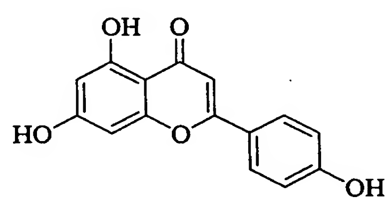
17β-HSD, which catalyses the final step in estrogens and androgens biosynthesis, also appeared as a target for estrogen deprivation strategies. This enzyme is responsible for the interconversion of the oxidized form (less active) and the reduced form (more active) of steroids. Its activity directly supports the growth and development of estrogen dependent tumours since it preferably reduces estrone into estradiol[25] and in a minor extend, *via* the conversion of the androgen DHEA into androstenediol (Adiol), which has recently been proven to have estrogenic properties and to be able to bind to the estrogen receptor.[26]

17β-HSD belongs to a family of isoenzymes, 11 of which have been so far identified and cloned.[27] Each type has a selective substrate affinity and directional activity which means that selectivity of drug action has to be achieved. 17β-HSD type 1 is the isotype that catalyses the interconversion of estrone and estradiol.

Unlike STS, only few 17β-HSD inhibitors have been reported. Most of the steroidal inhibitors for 17β-HSD type 1 have in common a D-ring modified structure. Estradiol derivatives which contain a side-chain with a good leaving group at the 16α-position have been shown to be a potent class of inhibitors. In particular, 16α-(bromoalkyl)-estradiol[28] where the side-chains exhibit high reactivity towards nucleophilic amino-acids residues in the active site of the enzyme were found to be promising irreversible inhibitors. Analogues containing short bromoalkyl moieties at position 16 exhibited the highest activity with 16α-(Bromopropyl)-estradiol, followed by 16α-(Bromobutyl)-estradiol, the most potent of the series (**3** and **4**, Figure 6). They, however, turned out to be pure agonists of the estrogen receptor.



3 R = $(CH_2)_3Br$
4 R = $(CH_2)_4Br$



Apigenin

Figure 6. 17β-HSD type 1 inhibitors: 16α-(bromopropyl)-estradiol, **3**; 16α-(bromopropyl)-estradiol, **4** and a flavone derivative, apigenin.

Aspects of the invention are defined in the appended claims.

In an attempt to eliminate the intrinsic estrogenicity of potent inhibitors and possibly at the same time engineer antiestrogenic properties into the molecule, several 16α-(bromalkyl)-estradiol derivatives bearing the C7α-alkylamide side chain of the known antiestrogen ICI 164384 were synthesised.[29] However, rather poor inhibition of 17β-HSD type 1 was obtained, with estrogenic and antiestrogenic properties not completely abolished or introduced respectively.

In parallel, non-steroidal inhibitors of 17β-HSD type 1 have been designed. Flavonoids, which are structurally similar to estrogens, are able to bind to the estrogen receptor with estrogenic or anti-estrogenic activities.[30] Their action on aromatase activity is well documented and in recent studies, they were found to reduce the conversion of estrone into estradiol catalysed by 17β-HSD type 1.[31] Flavone derivatives, such as apigenin (Figure 6) emerged from a SAR study as a promising compounds with some inhibitory activity on 17β-HSD type 1 without being estrogenic at the inhibitory concentration.[32]

I – 3 –Project

While research in the area of STS has generated several highly potent inhibitors, one of which is entering the clinic, 17β-HSD inhibitor design remains a field still ripe for development. To the best of our knowledge, 16α-(bromopropyl)-estradiol is the most potent inhibitor of 17β-HSD type 1 which suggests that the D-ring of the steroidal skeleton may play a major role in recognition of the substrate by the enzyme. However, 16α-(bromopropyl)-estradiol is estrogenic and most of the attempts to reduce its estrogenicity have either failed or resulted in a decrease in its activity.

A potent 17β-HSD type 1 inhibitor, free from agonist activity but possessing anti-estrogenic activity, would be a novel type of agent for the treatment of HDBC since it would act as dual suppresser of estrogen synthesis and action. It is therefore proposed that attempts to develop such an agent could be focused around the structural features of **3** (or **4**) with the addition of some specific modifications aiming at inducing non or antiestrogenic properties.

In order to decrease the affinity of the target molecule for the estrogen receptor and minimizing the chances estrogen-agonism induced by the drug, it was proposed to replace the 17β-hydroxyl function by a carbonyl group. Estradiol has indeed a 10-fold greater proliferative effect on breast tumour cells than estrone suggesting the estrogenicity of 17β-hydroxylated compounds.[33] Optimisation of the non estrogenic properties of these compounds can also be performed by introducing of a methoxy function at position 2 of the A-ring since 2-methoxyestrogens are known to be less estrogenic than their parent estrogens. They could also confer additional properties to the target compounds since they can inhibit tumour growth and angiogenesis.[34]

While the side-chain on the D-ring had to be retained since it is responsible for the activity, the strategy to induce it had to allow more versatility suggesting the need to modify the D-ring itself. Side-chains to be introduced include short to long alkyl moieties or bulky hydrophobic substituents whose effect on the activity of the enzyme can be related to the presence/absence of a hydrophobic pocket. Other types of side-chains such as bromoalkyl or cyclopropyl moieties could potentially interact with a nucleophilic amino-acid residue of the active side and unsaturations could confer rigidity to the side-chains whose orientation in the active site might be a determining factor for inhibition of the enzyme.

Finally, it was decided that the hydroxyl on the A-ring could be sulfamoylated, resulting in a molecule bearing close resemblance to EMATE. This would allow us to explore the concept of dual STS/17β-HSD inhibition given that the aryl-*O*-sulfamate moiety is the active pharmacophore for STS inhibition.

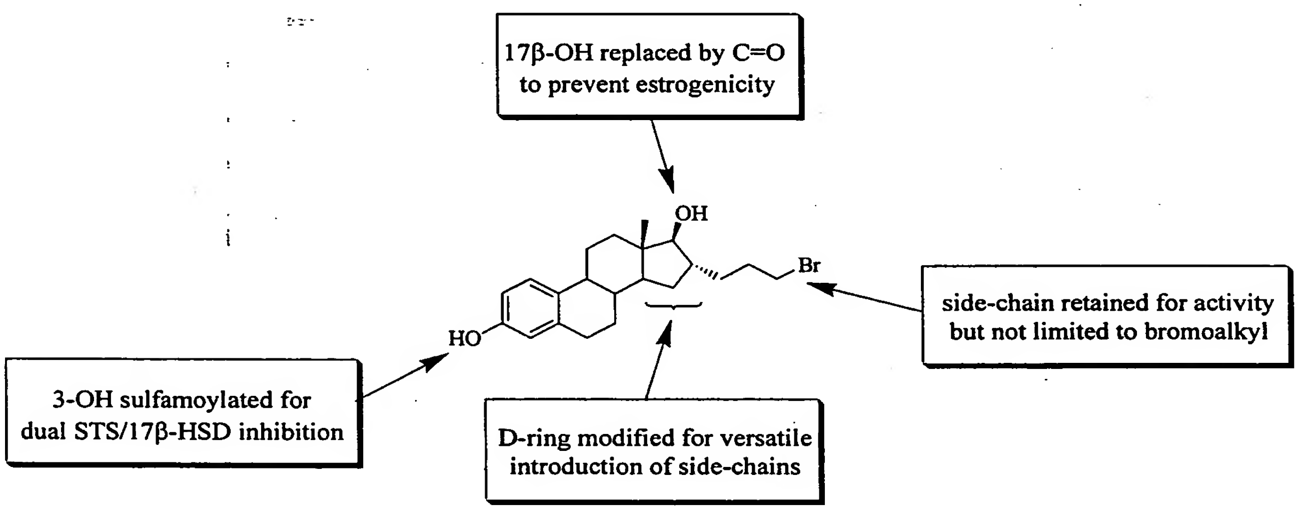
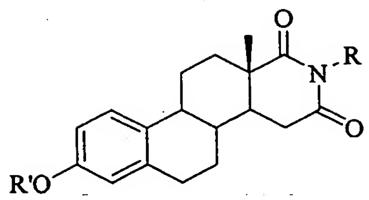


Figure 7. Proposed modifications on the molecule **3** for the design of non/anti-estrogenic inhibitors of 17β-HSD type 1 having potential STS inhibitory effects.

In order to achieve these requirements summarized on Figure 7, compound **5** (Figure 8) was postulated as a good candidate. With a structurally modified D-ring, it affords a novel approach to 17β-HSD type 1 inhibition having also the advantage over the above derivative of estradiol to allow a very easy introduction of side-chains on the N-imido atom of the D-ring. It can also be accessed in one step from benzyl marrianolic acid[35] which has been synthesized in our group from another project.



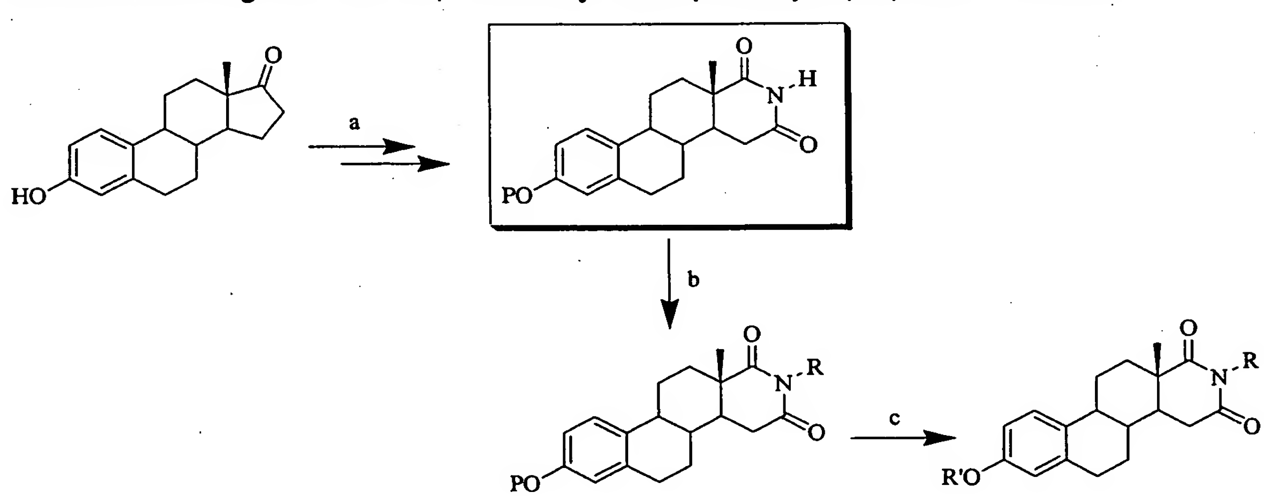
5

Figure 8. New target molecules for 17β-HSD type 1 and/or STS inhibition. 3-Hydroxy-16,17-seco-estra-1,3,5(10)-triene-16,17-imide, **5** (R = R' = H) and its parents (R = side-chain and R' = H or SO_2NH_2)

II – Synthetic strategies

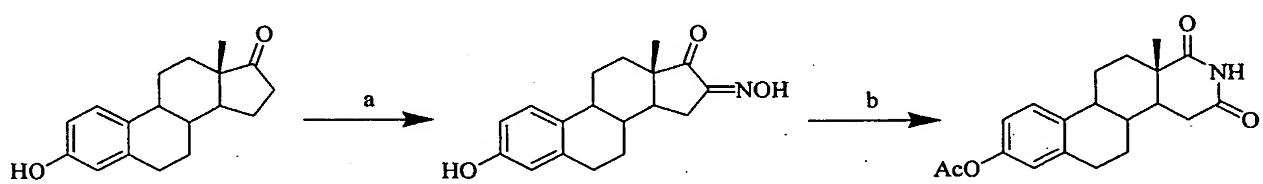
In order to establish a structure activity relationship for the family of molecules derived from **5**, an efficient synthetic pathway had to be developed, enabling an easy and effective introduction of a wide variety of side-chains on the D-ring.

The most logical approach, allowing versatility during the synthesis of the targets, is to consider the introduction of the side-chains on the D-ring after its conversion into a piperidine dione moiety. It was therefore proposed that, once protected at its C3-position, compound **5** would be a key intermediate for the synthesis of the targets since introduction of the side-chains can easily be performed in one step *via* N-alkylation. Subsequent deprotection and sulfamoylation would then yield the final phenolic compounds and sulfamates derivatives. Supposing that the key intermediate (framed) is accessible starting from estrone, a crude synthetic pathway is proposed in Scheme 1.



Scheme 1. Proposed synthetic approach to access the target molecules from commercially available estrone.
P = protecting group, R = side-chain, R' = H or SO_2NH_2.
(a) D-ring modification, protection; (b) alkylation; (c) deprotection, sulfamoylation.

The use of rearrangements in order to modify the D-ring of steroids have often been reported in the literature. Jindal et al. have proposed the access to the acetylated derivative of **5** *via* a Beckmann rearrangement of 16-oximino-estrone **6** (Scheme 2)[37], which we decided to investigate.



E1 6 7

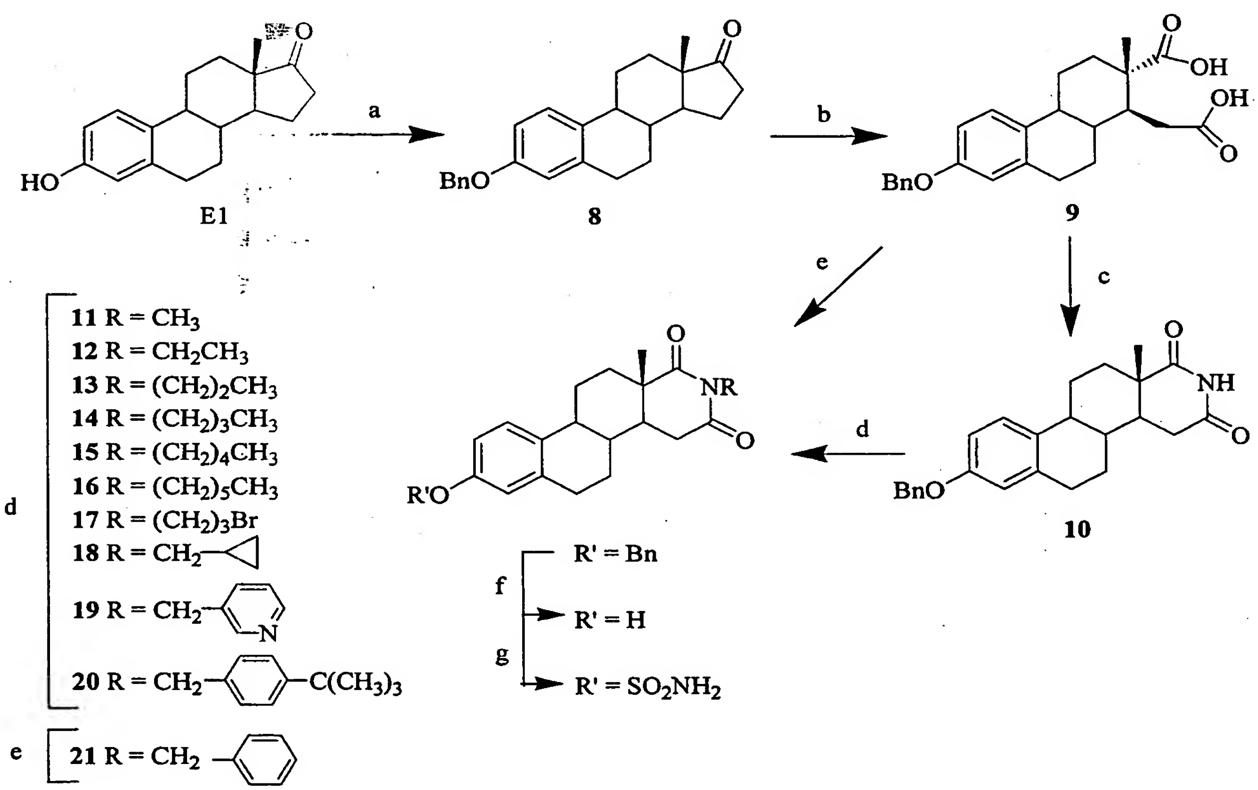
Scheme 2. Literature method for the synthesis of **7**.
Reagents: (a) $KOC(CH_3)_3$, $(CH_3)_2CH(CH_2)_2ONO$; (b) Ac_2O/ACOH, reflux.

Deprotonation of estrone was performed at room temperature under the action of potassium *tert*-butoxide, freshly prepared by dissolving potassium metal in anhydrous 2-methyl-propan-2-ol. Addition of an excess of isoamyl nitrite gave the keto oxime **6** with a yield of 63%. Beckmann rearrangement of the latter was carried out under refluxing condition of a mixture of acetic acid and acetic anhydride to give **7**, isolated with a yield of 57%.

The D-ring modified structure of **7** was fully established and confirmed using spectroscopic methods. Characteristic vibrational bands for the imide system were shown at 1725 and 1690 cm^{-1} on the IR spectrum of the compound and the NH exchangeable proton appeared at 10.64 ppm as a singlet on the ^1H NMR spectrum. The quaternary carbons C17 and C18 had a characteristic downfield chemical shifts at 171.9 and 178.7 ppm on the ^{13}C NMR spectrum.

While the Beckmann rearrangement of **6** has the advantage of yielding the intermediate **7** in two steps from estrone, the overall yield (36%) is rather poor, although comparable with those reported in the literature. It was therefore decided to develop another strategy which would provide **7** in much higher yields.

Modifications of the D-ring through its subsequent cleavage and closure was proposed as an alternative to access derivatives of **5**. The D-ring of protected estrone can indeed be opened *via* the haloform reaction[35] and closed by thermal condensation with an amine to yield piperidine dione D-ring derivatives of estrone. Scheme 3 summarizes the pathway envisaged as well as the side-chains to be introduced by N-alkylation.



Scheme 3. Alternative method for the synthesis of **10-21** *via* benzyl marrianolic acid **9**. Reagents: (a) NaH/DMF, BnBr, 80°C; (b) I_2, KOH, MeOH then KOH reflux; (c) urea, 180°C; (d) NaH/DMF, RX; (e) RNH_2, 180°C; (f) Pd/C, H_2, MeOH/THF; (g) $ClSO_2NH_2$/DMA.

By reacting benzyl-estrone **8**, which was easily prepared by benzylation of estrone, with

an excess of base (potassium hydroxide) and iodine, the methylene ketone function was bis-halogenated then cleaved. Full conversion into the di-carboxylic acid was achieved by refluxing in a concentrated solution of KOH. Benzyl marrianolic acid **9**, which was isolated with an optimised yield of 75%, was then subjected to a thermal cyclisationg in presence of urea. This condensation reaction, which leads to the formation of a favorized 6-membered ring, occurs when heating the reagents at 180°C for a short period of time. The resulting D-ring modified steroid **10** was obtained in high yield (80-89%) giving an overall yield for the synthesis the intermediate **10** of 55%. Thus, despite the presence of an additional step, this alternative method represents a significant improvement over the literature method.

Since imides are too weak bases to attack alkyl halides, they must first be converted into their conjugate bases before undergoing N-alkylation. To this end, **10** was deprotonated using sodium hydride in DMF before reacting, *via* most likely an S_N2 reaction, with various alkylating agents. Following this method, a large number of side-chains have been successfully introduced. Compounds **11-21** were obtained with yields ranging from 75 to 97% and an average reaction time of 2 hours.

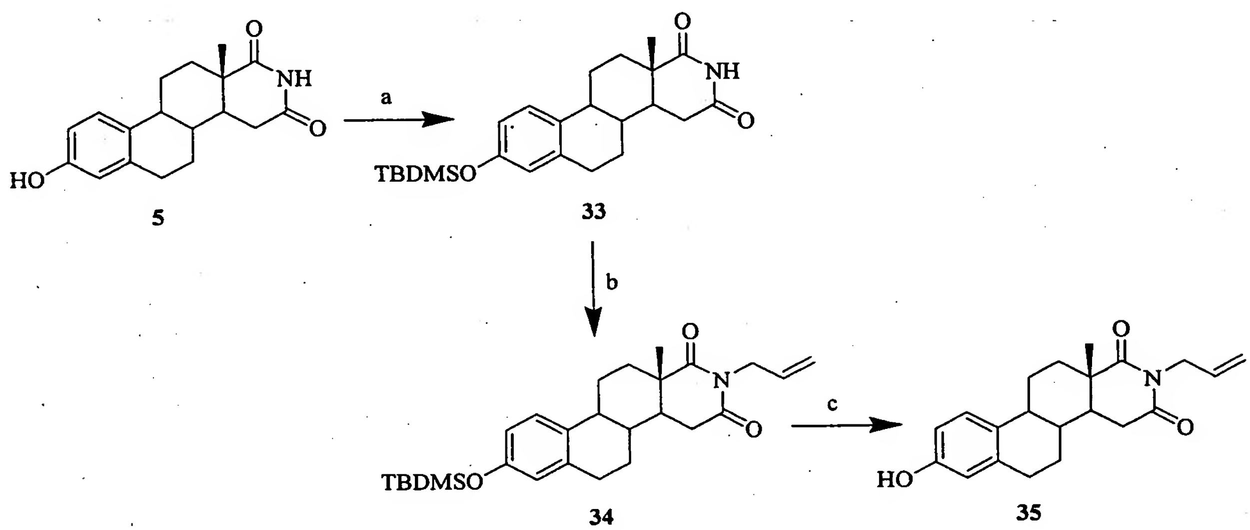
N-alkylated compounds can also be directly accessed from benzyl marrianolic acid when this latter is heated in the presence of an alkylamine. The derivative **21** (R = benzyl) was synthesized this way, however, the yield of the reaction was moderate (65%). It was therefore proposed that the direct method from BMA would be employed when exceptionally the alkyl halides are commercially unavailable or deemed unreactive towards the N-alkylation of **10**.

Benzyl ether of compounds **11-21** was then cleaved by catalytic hydrogenation using Pd/C to afford the series of hydroxylated targets **22-32** with high yields.

For the introduction of unsaturated side chains, another strategy had to be developed since the last step of Scheme 3 involves a hydrogenolysis which is likely to debenzylate and hydrogenate the unsaturated group concurrently. Although some selective methods for the reduction of benzyl-protected hydroxyl function have been reported,[38] protection of **5** with a *tert*-butyl-dimethylsilyl group before N-alkylation is a simple effective alternative method

Protection of the phenol function of **5** was conducted in presence of *tert*-butyl-dimethylsilyl chloride and imidazole *via* the formation of an intermediate reactive species.

Alkylation of the resulting protected compound **33** with allyl bromide easily yielded **34**, which was deprotected with tetrabutylammonium fluoride. This particular approach (Scheme 4)., developed for the introduction of an allyl moiety, should also be applicable to induce other unsaturated groups on the N-atom.



Scheme 4. Synthesis of the N-allyl derivative of **5**.

Reagents: (a) TBDMSCl/Imidazole, DMF; (b) NaH/DMF, CH_2CHCH_2Br; (c) TBAF/THF.

Sulfamoylation of the hydroxylated compounds was performed following a recent procedure described by Okada et al.[39] in which sulfamoylation of phenolic compounds is conducted in the aprotic solvent dimethylacetamide in the absence of base. In general, this method, which requires only a slight excess of sulfamoyl chloride, gives a better yield of sulfamates than the usual procedure where NaH/DMF are employed. It is proposed that DMF could undergo a side-reaction with sulfamoyl chloride, which cannot occur with DMA, because of the unavailability of a formyl proton. It was also found that elimination of a base in the reaction conditions led to the highest yields and that probably DMA worked as a moderate base.

Following a procedure developed in our group, hydroxylated derivatives **5**, **22-32** and **35** were sulfamoylated in the presence of 2.2 equivalents of sulfamoyl chloride in DMA. Compounds **36-48** were mostly obtained in high yields after short reaction time. However, sulfamoylation of **28** had to be performed according to the initial NaH/DMF method since a side-reaction occurred between the bromobutyl side-chain and sulfamoyl

chloride when DMA was the solvent. Unexpectedly, the side-product was found to be a sulfamate of **5** bearing a chlorobutyl side-chain. HPLC analysis of the crude showed that the side-product formed in the same proportions as that of the expected product **43**. Despite the presence of two well- separated peaks at 5.5 min and 6.50 min (elution MeOH/H_2O 68:32) on the HPLC run, attempt to separate both products by flash chromatography or recrystallization failed. They were therefore isolated using preparative HPLC and characterized by ^1H NMR and accurate mass spectroscopy.

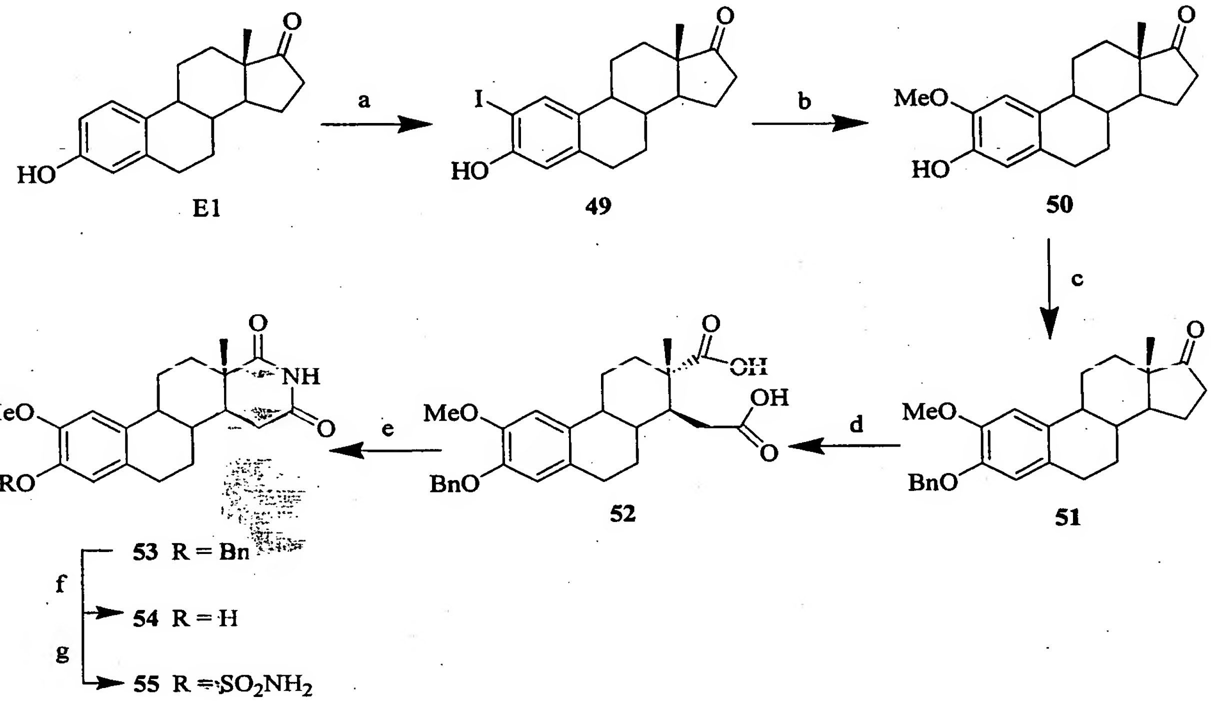
When the reaction was carried out using NaH/DMF and 6 equivalents of sulfamoyl chloride, **43** was isolated with a yield of 81% as the sole product of the reaction. In this reaction, chlorine resulting from the nucleophilic attack of the phenolate ion on sulfamoyl chloride is trapped as HCl and is therefore unable to react with the bromobutyl side-chain.

Finally, a 2-methoxy derivative of **5** and its sulfamate were synthesized following the same sequence of reaction as that described in Scheme 3, starting from 2-methoxy-estrone. This latter was prepared according to an efficient two steps synthesis developed in our group, where introduction of a methoxy group on position 2 relies on the nucleophilic displacement of an halogen atom by a methoxyde anion.

To this end, 2-iodo-estrone **49** was prepared by treating estrone with mercuric acetate and iodine in acetic acid.[40] The selective halogenation at position 2 was complete within 2 hours at room temperature with an overall yield of 56% after successive recrystallizations. 2-Iodo-estrone then reacted with a large excess of a freshly prepared solution of sodium methoxyde, in presence of copper chloride in refluxing pyridine[41] and gave 2-methoxy-estrone **50** with a yield of 75%. This method has the advantage of not involving any protecting group and gives good overall yield (42%) for the synthesis of 2-methoxy-estrone in two steps from estrone.

After benzylation, the resulting compound **51** was subjected to the haloform reaction. A limited solubility of **51** in methanol led to a poor, non-optimised yield of 18% for the synthesis of **52**. Ring closure in presence of urea gave **53** with a yield of 59% and subsequent deprotection gave the final products **54**. Sulfamoylation of **54** had to be conducted using NaH/DMF with a large excess of sulfamoyl chloride since a the lack of reactivity was observed when the reaction was carried out in DMA. This can be due to

the steric hindrance of position 3 resulting from the presence of the methoxy group at position 2.



Scheme 5. Synthesis of the 2-methoxy derivative of **5** and its sulfamate.
Reagents: (a) $Hg(OAc)_2$, I_2, AcOH/THF; (b) $CuCl_2$/Pyridine, NaOMe, reflux; (c) $KOC(CH_3)_3$/DMF, BnBr; (d) I_2, KOH, MeOH then KOH reflux; (e) urea, 180°C; (f) Pd/C, H_2, MeOH/THF; (g) $ClSO_2NH_2$/DMA.

III – Results and discussion

The compounds of the present invention are found to act as HSD inhbitors.

V – Summary

Breast cancer is a disease of major importance in Europe and Northern America. In Britain, it kills more people than any other type of cancer. Hormone dependant breast cancer represents about two third of those cases in postmenopausal women; it corresponds to a type of breast cancer in which tumours rely on estrogens for their growth and development.

Endocrine therapy, where estrogen circulating levels are controlled *via* the use of drugs

that inhibit one or several enzymatic pathway in estrogen biosynthesis, is the response for HDBC. Different targets can be considered and most of the work has been done around antiestrogens and aromatase inhibitors. The enzymes steroid sulfatase and 17β-HSD type 1 have later emerged as potent targets.

While several potent inhibitors have been developed for STS, 17β-HSD type 1 has not raised as much interest and only few active molecules have been reported. Relying on the fact that D-ring derivatives of EMATE are potent inhibitors of 17β-HSD type 1, we initiated the design and synthesis of analogs of EMATE with reduced estrogenicity. This has led to a series of compounds where the D-ring is a piperidine dione moiety and where the N-atom is bearing a variety of side-chains.

In one aspect the present invention provides novel compounds.

In one aspect the present invention provides use of a compound in the manufacture of a medicament to inhibit HSD activity.

By HSD it is meant 17β hydroxy steroid dehydrogenase. In one aspect the 17β hydroxy steroid dehydrogenase is EC 1.1.1.62

Preferably the HSD is of Type 1, 3, 5 and/or 7. Preferably the HSD converts estrone (ketone) to estradiol (hydroxy).

Preferably the HSD is of Type 2 and/or 8. Preferably the HSD converts estradiol (hydroxy) to estrone (ketone).

In one aspect the present invention provides use of a compound of the present invention in the manufacture of a medicament for use in the therapy of a condition or disease associated with HSD.

In one aspect the present invention provides use of a compound of the present invention in the manufacture of a medicament for use in the therapy of a condition or disease associated adverse HSD levels.

In one aspect the present invention provides a method of inhibiting HSD in a patient in need of same comprising administering a compound of the present invention.

SOME ADVANTAGES

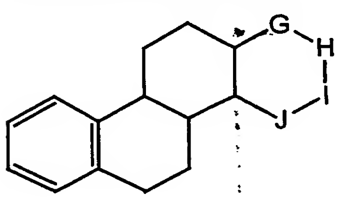
One key advantage of the present invention is that the compounds of the present invention can act as HSD inhibitors.

Another advantage of the compounds of the present invention is that they may be potent HSD inhibitors *in vivo*.

Some of the compounds of the present invention are also advantageous in that they may be orally active.

The compound of or for use in the present invention may be substituted with additional substituents to those specifically recited in the general formulae of the present specification or may contain one or more further bonds/degrees of unsaturation.

A typical compound is of the formula



In general terms the ring system of the compound of the present invention may contain a variety of non-interfering substituents. In particular, the ring system may contain one or more cycloalkyl, alkenyl, aryl, hydroxy, alkyl especially lower (C_1-C_6) alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and other pentyl isomers, and n-hexyl and other hexyl isomers, alkoxy especially lower (C_1-C_6) alkoxy, e.g. methoxy, ethoxy, propoxy etc., alkinyl, e.g. ethinyl, or halogen, e.g. fluoro substituents. Within the values alkyl, cycloalkyl, alkenyl and aryl substituted groups are included containing as substituents therein one or more groups which do not interfere with the inhibitory activity of the compound in question. Exemplary non-interfering substituents include hydroxy, amino, halo, alkoxy, alkyl and aryl.

By the term "substituted nitrogen" it is meant the nitrogen is attached to a group other than H. Preferably the N is attached to a hydrocarbyl group.

The term "hydrocarbyl group" as used herein means a group comprising at least C and H and may optionally comprise one or more other suitable substituents. Examples of such substituents may include halo, alkoxy, nitro, an alkyl group, a cyclic group etc. In addition to the possibility of the substituents being a cyclic group, a combination of substituents may form a cyclic group. If the hydrocarbyl group comprises more than one C then those carbons need not necessarily be linked to each other. For example, at least two of the carbons may be linked via a suitable element or group. Thus, the hydrocarbyl group may contain hetero atoms. Suitable hetero atoms will be apparent to those skilled in the art and include, for instance, sulphur, nitrogen and oxygen. A non-limiting example of a hydrocarbyl group is an acyl group.

A typical hydrocarbyl group is a hydrocarbon group. Here the term "hydrocarbon" means any one of an alkyl group, an alkenyl group, an alkynyl group, which groups may be linear, branched or cyclic, or an aryl group. The term hydrocarbon also includes those groups but wherein they have been optionally substituted. If the hydrocarbon is a branched structure having substituent(s) thereon, then the substitution may be on either the hydrocarbon backbone or on the branch; alternatively the substitutions may be on the hydrocarbon backbone and on the branch.

Typical hydrocarbyl groups are C_1-C_{10} hydrocarbyl, C_1-C_5 hydrocarbyl or C_1-C_3 hydrocarbyl.

Typical hydrocarbon groups are C_1-C_{10} hydrocarbon, C_1-C_5 hydrocarbon, C_1-C_3 hydrocarbon, alkyl groups, C_1-C_{10} alkyl, C_1-C_5 alkyl and C_1-C_3 alkyl.

The hydrocarbyl/hydrocarbon/alkyl may be straight chain or branched and/or may be saturated or unsaturated.

The term "oxyhydrocarbyl" group as used herein means a group comprising at least C, H and O and may optionally comprise one or more other suitable substituents. Examples of such substituents may include halo-, alkoxy-, nitro-, an alkyl group, a cyclic group etc. In addition to the possibility of the substituents being a cyclic group, a combination of

substituents may form a cyclic group. If the oxyhydrocarbyl group comprises more than one C then those carbons need not necessarily be linked to each other. For example, at least two of the carbons may be linked *via* a suitable element or group. Thus, the oxyhydrocarbyl group may contain hetero atoms. Suitable hetero atoms will be apparent to those skilled in the art and include, for instance, sulphur and nitrogen.

In one embodiment of the present invention, the oxyhydrocarbyl group is a oxyhydrocarbon group.

Here the term "oxyhydrocarbon" means any one of an alkoxy group, an oxyalkenyl group, an oxyalkynyl group, which groups may be linear, branched or cyclic, or an oxyaryl group. The term oxyhydrocarbon also includes those groups but wherein they have been optionally substituted. If the oxyhydrocarbon is a branched structure having substituent(s) thereon, then the substitution may be on either the hydrocarbon backbone or on the branch; alternatively the substitutions may be on the hydrocarbon backbone and on the branch.

Typically, the oxyhydrocarbyl group is of the formula $C_{1-6}O$ (such as a $C_{1-3}O$).

The compounds of the present invention may be in the form of a salt.

In a further aspect the present invention provides a pharmaceutical composition comprising a novel compound as described herein optionally admixed with a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

In a further aspect the present invention provides a novel compound as described herein for use in medicine.

THERAPY

The compounds of the present invention may be used as therapeutic agents – i.e. in therapy applications.

The term "therapy" includes curative effects, alleviation effects, and prophylactic effects.

The therapy may be on humans or animals, preferably female animals.

PHARMACEUTICAL COMPOSITIONS

In one aspect, the present invention provides a pharmaceutical composition, which comprises a compound according to the present invention and optionally a pharmaceutically acceptable carrier, diluent or excipient (including combinations thereof).

The pharmaceutical compositions may be for human or animal usage in human and veterinary medicine and will typically comprise any one or more of a pharmaceutically acceptable diluent, carrier, or excipient. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A.R.Gennaro edit. 1985). The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as - or in addition to - the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s).

Preservatives, stabilisers, dyes and even flavouring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

There may be different composition/formulation requirements dependent on the different delivery systems. By way of example, the pharmaceutical composition of the present invention may be formulated to be delivered using a mini-pump or by a mucosal route, for example, as a nasal spray or aerosol for inhalation or ingestable solution, or parenterally in which the composition is formulated by an injectable form, for delivery, by, for example, an intravenous, intramuscular or subcutaneous route. Alternatively, the formulation may be designed to be delivered by both routes.

Where the agent is to be delivered mucosally through the gastrointestinal mucosa, it should be able to remain stable during transit though the gastrointestinal tract; for

example, it should be resistant to proteolytic degradation, stable at acid pH and resistant to the detergent effects of bile.

Where appropriate, the pharmaceutical compositions can be administered by inhalation, in the form of a suppository or pessary, topically in the form of a lotion, solution, cream, ointment or dusting powder, by use of a skin patch, orally in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents, or they can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For parenteral administration, the compositions may be best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or monosaccharides to make the solution isotonic with blood. For buccal or sublingual administration the compositions may be administered in the form of tablets or lozenges which can be formulated in a conventional manner.

COMBINATION PHARMACEUTICAL

The compound of the present invention may be used in combination with one or more other active agents, such as one or more other pharmaceutically active agents.

By way of example, the compounds of the present invention may be used in combination with other HSD inhibitors.

ADMINISTRATION

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject and it will vary with the age, weight and response of the particular patient. The dosages below are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited.

The compositions of the present invention may be administered by direct injection. The composition may be formulated for parenteral, mucosal, intramuscular, intravenous, subcutaneous, intraocular or transdermal administration. Depending upon the need, the

agent may be administered at a dose of from 0.01 to 30 mg/kg body weight, such as from 0.1 to 10 mg/kg, more preferably from 0.1 to 1 mg/kg body weight.

By way of further example, the agents of the present invention may be administered in accordance with a regimen of 1 to 4 times per day, preferably once or twice per day. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Aside from the typical modes of delivery – indicated above – the term "administered" also includes delivery by techniques such as lipid mediated transfection, liposomes, immunoliposomes, lipofectin, cationic facial amphiphiles (CFAs) and combinations thereof. The routes for such delivery mechanisms include but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical, or sublingual routes.

The term "administered" includes but is not limited to delivery by a mucosal route, for example, as a nasal spray or aerosol for inhalation or as an ingestable solution; a parenteral route where delivery is by an injectable form, such as, for example, an intravenous, intramuscular or subcutaneous route.

Thus, for pharmaceutical administration, the HSD inhibitors of the present invention can be formulated in any suitable manner utilising conventional pharmaceutical formulating techniques and pharmaceutical carriers, adjuvants, excipients, diluents etc. and usually for parenteral administration. Approximate effective dose rates may be in the range from 1 to 1000 mg/day, such as from 10 to 900 mg/day or even from 100 to 800 mg/day depending on the individual activities of the compounds in question and for a patient of average (70Kg) bodyweight. More usual dosage rates for the preferred and more active compounds will be in the range 200 to 800 mg/day, more preferably, 200 to 500 mg/day, most preferably from 200 to 250 mg/day. They may be given in single dose regimes, split dose regimes and/or in multiple dose regimes lasting over several days. For oral administration they may be formulated in tablets, capsules, solution or suspension containing from 100 to 500 mg of compound per unit dose. Alternatively and preferably the compounds will be formulated for parenteral administration in a suitable parenterally

administrable carrier and providing single daily dosage rates in the range 200 to 800 mg, preferably 200 to 500, more preferably 200 to 250 mg. Such effective daily doses will, however, vary depending on inherent activity of the active ingredient and on the bodyweight of the patient, such variations being within the skill and judgement of the physician.

The compounds of the present invention may be useful in the manufacture of a medicament for revealing an endogenous glucocorticoid-like effect.

OTHER THERAPIES

It is also to be understood that the compound/composition of the present invention may have other important medical implications.

For example, the compound or composition of the present invention may be useful in the treatment of the disorders listed in WO-A-99/52890 – *viz*:

In addition, or in the alternative, the compound or composition of the present invention may be useful in the treatment of the disorders listed in WO-A-98/05635. For ease of reference, part of that list is now provided: cancer, inflammation or inflammatory disease, dermatological disorders, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia, anorexia, acute infection, HIV infection, shock states, graft-versus-host reactions, autoimmune disease, reperfusion injury, meningitis, migraine and aspirin-dependent anti-thrombosis; tumour growth, invasion and spread, angiogenesis, metastases, malignant, ascites and malignant pleural effusion; cerebral ischaemia, ischaemic heart disease, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma, multiple sclerosis, neurodegeneration, Alzheimer's disease, atherosclerosis, stroke, vasculitis, Crohn's disease and ulcerative colitis; periodontitis, gingivitis; psoriasis, atopic dermatitis, chronic ulcers, epidermolysis bullosa; corneal ulceration, retinopathy and surgical wound healing; rhinitis, allergic conjunctivitis, eczema, anaphylaxis; restenosis, congestive heart failure, endometriosis, atherosclerosis or endosclerosis.

In addition, or in the alternative, the compound or composition of the present invention may be useful in the treatment of disorders listed in WO-A-98/07859. For ease of

reference, part of that list is now provided: cytokine and cell proliferation/differentiation activity; immunosuppressant or immunostimulant activity (e.g. for treating immune deficiency, including infection with human immune deficiency virus; regulation of lymphocyte growth; treating cancer and many autoimmune diseases, and to prevent transplant rejection or induce tumour immunity); regulation of haematopoiesis, e.g. treatment of myeloid or lymphoid diseases; promoting growth of bone, cartilage, tendon, ligament and nerve tissue, e.g. for healing wounds, treatment of burns, ulcers and periodontal disease and neurodegeneration; inhibition or activation of follicle-stimulating hormone (modulation of fertility); chemotactic/chemokinetic activity (e.g. for mobilising specific cell types to sites of injury or infection); haemostatic and thrombolytic activity (e.g. for treating haemophilia and stroke); antiinflammatory activity (for treating e.g. septic shock or Crohn's disease); as antimicrobials; modulators of e.g. metabolism or behaviour; as analgesics; treating specific deficiency disorders; in treatment of e.g. psoriasis, in human or veterinary medicine.

In addition, or in the alternative, the composition of the present invention may be useful in the treatment of disorders listed in WO-A-98/09985. For ease of reference, part of that list is now provided: macrophage inhibitory and/or T cell inhibitory activity and thus, anti-inflammatory activity; anti-immune activity, i.e. inhibitory effects against a cellular and/or humoral immune response, including a response not associated with inflammation; inhibit the ability of macrophages and T cells to adhere to extracellular matrix components and fibronectin, as well as up-regulated fas receptor expression in T cells; inhibit unwanted immune reaction and inflammation including arthritis, including rheumatoid arthritis, inflammation associated with hypersensitivity, allergic reactions, asthma, systemic lupus erythematosus, collagen diseases and other autoimmune diseases, inflammation associated with atherosclerosis, arteriosclerosis, atherosclerotic heart disease, reperfusion injury, cardiac arrest, myocardial infarction, vascular inflammatory disorders, respiratory distress syndrome or other cardiopulmonary diseases, inflammation associated with peptic ulcer, ulcerative colitis and other diseases of the gastrointestinal tract, hepatic fibrosis, liver cirrhosis or other hepatic diseases, thyroiditis or other glandular diseases, glomerulonephritis or other renal and urologic diseases, otitis or other oto-rhino-laryngological diseases, dermatitis or other dermal diseases, periodontal diseases or other dental diseases, orchitis or epididimo-orchitis, infertility, orchidal trauma or other immune-related testicular diseases, placental dysfunction, placental insufficiency, habitual abortion, eclampsia, pre-eclampsia and

other immune and/or inflammatory-related gynaecological diseases, posterior uveitis, intermediate uveitis, anterior uveitis, conjunctivitis, chorioretinitis, uveoretinitis, optic neuritis, intraocular inflammation, e.g. retinitis or cystoid macular oedema, sympathetic ophthalmia, scleritis, retinitis pigmentosa, immune and inflammatory components of degenerative fondus disease, inflammatory components of ocular trauma, ocular inflammation caused by infection, proliferative vitreo-retinopathies, acute ischaemic optic neuropathy, excessive scarring, e.g. following glaucoma filtration operation, immune and/or inflammation reaction against ocular implants and other immune and inflammatory-related ophthalmic diseases, inflammation associated with autoimmune diseases or conditions or disorders where, both in the central nervous system (CNS) or in any other organ, immune and/or inflammation suppression would be beneficial, Parkinson's disease, complication and/or side effects from treatment of Parkinson's disease, AIDS-related dementia complex HIV-related encephalopathy, Devic's disease, Sydenham chorea, Alzheimer's disease and other degenerative diseases, conditions or disorders of the CNS, inflammatory components of stokes, post-polio syndrome, immune and inflammatory components of psychiatric disorders, myelitis, encephalitis, subacute sclerosing pan-encephalitis, encephalomyelitis, acute neuropathy, subacute neuropathy, chronic neuropathy, Guillaim-Barre syndrome, Sydenham chora, myasthenia gravis, pseudo-tumour cerebri, Down's Syndrome, Huntington's disease, amyotrophic lateral sclerosis, inflammatory components of CNS compression or CNS trauma or infections of the CNS, inflammatory components of muscular atrophies and dystrophies, and immune and inflammatory related diseases, conditions or disorders of the central and peripheral nervous systems, post-traumatic inflammation, septic shock, infectious diseases, inflammatory complications or side effects of surgery, bone marrow transplantation or other transplantation complications and/or side effects, inflammatory and/or immune complications and side effects of gene therapy, e.g. due to infection with a viral carrier, or inflammation associated with AIDS, to suppress or inhibit a humoral and/or cellular immune response, to treat or ameliorate monocyte or leukocyte proliferative diseases, e.g. leukaemia, by reducing the amount of monocytes or lymphocytes, for the prevention and/or treatment of graft rejection in cases of transplantation of natural or artificial cells, tissue and organs such as cornea, bone marrow, organs, lenses, pacemakers, natural or artificial skin tissue.

The present invention will now be described in further detail in the following examples.

EXAMPLES

VI - Experimental

VI – 1 – General Methods

All chemicals were either purchased from Aldrich Chemical Co. (Gillingham, Dorset, UK) or Lancaster Synthesis (Morecambe, Lancashire, U.K.). All organic solvents of A. R. grade were supplied by Fisons plc (Loughborough, U.K.). Anhydrous *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA), respectively used for all *N*-alkylations and sulfamoylation reactions, were purchased from Aldrich and were stored under a positive pressure of N_2 after use. Sulfamoyl chloride was prepared by an adaptation of the method of Apel and Berger[48] and was stored as a solution in toluene as described by Woo et al.[16] An appropriate volume of this solution was freshly concentrated in vacuo immediately before use.

E1S and E1 were purchased from Sigma Chemical Co. (Poole, U.K.). [6,7-^{3}H]E1S (specific activity, 50 Ci/mmol) and [4-^{14}C]E1 (specific activity, 52 mCi/mmol) were purchased from New England Nuclear (Boston, MA). [6,7-^{3}H]E1 (specific activity, 97 Ci/mmol) was obtained from the Amersham International Radiochemical Centre (Amersham, U.K.).

Thin layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminium sheets silica gel 60 F_{254}, Art. No. 5554). Product(s) and starting material (SM) were detected by either viewing under UV light or treating with a methanolic solution of phosphomolybdic acid followed by heating. Flash column chromatography was performed on silica gel (Sorbsil C60). IR spectra were determined as KBr discs using a Perkin-Elmer Spectrum RXI FT-IR and peak positions are expressed in cm^{-1}. ^{1}H NMR and *DEPT*-edited ^{13}C NMR spectra were recorded with JMN-GX 400 NMR spectrometers, and chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS) as an internal standard. The following abbreviations are used to describe resonances in ^{1}H NMR and ^{13}C NMR spectra: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and combinations such as dd, doublet of doublets.

Chemical shifts for AB systems (δ_A and δ_B) were approximated by taking the middle of each doublet and the corresponding coupling constant labelled J_{AB} or J_{BA}. As an example, δ_A and δ_B were calculated following the formula shown in appendix 2 for compound **21**. HPLC analysis were performed on a Waters Millenium[32] instrument equipped with a Waters 996 PDA detector. The traces were recorded on a Waters Radialpack C18, 8×100 mm column eluted with a methanol/water gradient at 2 mL/min. Mass spectra were recorded at the Mass Spectrometry Service Center, University of Bath. FAB-MS were carried out using *m*-nitrobenzyl alcohol (NBA) as the matrix, and elemental analyses were performed by the Microanalysis Service, University of Bath. Melting points were determined using a Reichert-Jung Thermo Galen Kofler block and are uncorrected. The X-ray crystallographic study of **39** was carried out by Dr. M. Mahon in the Department of Chemistry, University of Bath and the data reported in appendix 3.

VI – 1 – 1 – Biological assays

All assays were performed at the Department of Endocrinology and Metabolic Medicine, Imperial College School of Medicine, St. Mary's Hospital, London by and in collaboration with Dr. A. Purohit and Pr. M. Reed.

VI – 1 – 2 - Preparation of sulfamoyl chloride

Formic acid (6 mL, 150 mmol) was added dropwise to a stirred solution of chlorosulfonyl isocyanate (25 g, 150 mmol) in 150 mL of freshly distilled toluene at 0°C under an atmosphere of N_2. The resulting white suspension was stirred overnight at room temperature under N_2 and the insoluble was filtered out of the solution under N_2 using a cannule. The filtrate was concentrated in vacuo to give a light brown crude of sulfamoyl chloride. A standard solution (ca 0.70 M) of sulfamoyl chloride was then prepared by dissolving the crude crystalline product in freshly distilled toluene and stored in the refrigerator under N_2. Prior to the reaction, formic acid was stirred overnight with boric anhydride and freshly distilled under N_2.

VI – 1 – 3 - General method for alkylation

Sodium hydride (60% dispersion in mineral oil, 1.2 eq) was added to a stirred solution of **10** in anhydrous DMF (15 mL) at 0°C under an atmosphere of N_2. After evolution of hydrogen had ceased, the parent alkylating agent (2 eq.) was added. The reaction mixture was stirred at room temperature and poured into water (50 mL). The resulting solution was extracted into ethyl acetate (50 mL). After further exhaustive washing with brine (4×25 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo. Fractionation of the crude product that obtained by flash chromatography gave the parents compounds **11-21**.

VI – 1 – 4 - General method for hydrogenolysis

Pd-C (10%) was added to a solution of **10-21** in MeOH/THF and the resulting suspension was hydrogenated at room temperature using a hydrogen-filled balloon. After removal of the supported catalyst by filtration and evaporation of the filtrate in vacuo, the product obtained was partially (analytical sample) or fully purified to give the parent compounds **5** and **22-32**.

VI – 1 – 5 - General method for sulfamoylation

To a stirred solution of sulfamoyl chloride (2.2 eq.) in DMA at 0°C under an atmosphere of N_2 was added **5, 22-32** and **35**. The reaction mixture was stirred under N_2 in which time it was allowed to warm to room temperature. It was then poured into cold brine (15 mL), and the resulting solution was extracted with ethyl acetate (2×20 mL). The organic layers were combined, washed with brine (6×20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product that obtained was fractionated by flash chromatography and/or recrystallized.

VI – 2 – Synthesis

V I– 2 – 1 – Synthesis of the D-ring modified steroidal moiety

16-oximino-estrone 6

To a stirred solution of potassium *tert*-butoxide under an atmosphere of N_2, freshly prepared by dissolving potassium metal (80 mg, 2.05 mmol) in 2 mL *tert*-butanol, estrone (200 mg, 740 mmol) was added. The reaction mixture was then stirred for 1 hour at room temperature under N_2 and isoamyl nitrite (180 μmol, 1.34 mmol) was added dropwise. The deep red mixture obtained was stirred overnight and then poured into water (20 mL). The resulting solution was extracted with ether (2×20 mL) and the aqueous layer was acidified with glacial acetic acid (10 mL) to give a light yellow precipitate. This was left separating for two hours after which the solid was filtered (140 mg, 63%): mp 223-225°C (lit. 226-227°C);[43] TLC (chloroform/acetone, 9:1) R_f 0.27 cf. R_f 0.69 (E1); IR (KBr) 3385 (NOH), 2920-2860 (aliph CH), 1735 (C=O), 1605-1500 (arom C=C) cm^{-1}; δ_H (DMSO-d$_6$, 400 MHz) 0.89 (3H, s, C-18-H_3), 1.30-2.85 (11H, m), 2.70-2.81 (2H, m, C-6-H_2), 6.46 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.52 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H), 7.05 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.2 Hz, C-1-H), 9.05 (1H, s, exchanged with D_2O, OH) and 12.39 (1H, s, exchanged with D_2O, NOH); δ_C (DMSO-d$_6$, 100.4 MHz) 14.09 (q, C-18), 25.09 (t), 25.46 (t), 26.18 (t), 29.02 (t), 30.92 (t), 37.20 (d), 43.20 (d), 44.59 (d), 48.50 (s, C-13), 112.70 (d), 114.83 (d), 125.82 (d), 129.59 (s), 136.88 (s), 154.84 (s, C-3 or C-16), 155.23 (s, C-3 or C-16) and 204.64 (s, C=O); MS *m/z* (FAB+) 453.2 [30, (M+H+NBA)$^+$], 300.1 [100, (M+H)$^+$]; MS *m/z* (FAB-) 451.3 [38, (M-H+NBA)$^-$], 298.2 [100, (M-H)$^-$]; Acc MS *m/z* (FAB+) 300.15963, $C_{18}H_{22}NO_3$ requires 300.15997. **CHN,**

3-Acetoxy-16-oximino-estrone

A suspension of **6** (150 mg, 501 mmol) in a mixture of 4.5 mL of glacial acetic acid and 7.5 mL of acetic anhydride was heated to reflux under an atmosphere of N_2 for 20 hours. The solvent mixture was then removed under reduced pressure and water was added. After basification with aqueous NaOH, the resulting solution was extracted with ethyl acetate (2×20 mL). The organic layer was separated, washed with water (2×15 mL), then

brine (2×15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **7** as a light yellow solid (97 mg, 57%): mp 189-193°C (lit. 196-198°C);[43] **CHN** TLC (chloroform/acetone, 9:1) R_f 0.68 cf. R_f 0.31 (**6**); IR (KBr) 3205 (NH), 2940-2860 (aliph CH), 1760 ($OCOCH_3$), 1725 (C=O), 1690 (C=O), 1610-1495 (arom C=C) cm^{-1}; δ_H (DMSO-d_6, 400 MHz) 1.11 (3H, s, C-18-H_3), 1.20-2.72 (11H, m), 2.77-2.84 (2H, m, C-6-H_2), 2.23 (3H, s, OAc), 6.81 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.87 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.5 Hz, C-2-H), 7.32 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.2 Hz, C-1-H) and 10.64 (1H, s, exchanged with D_2O, NH); δ_C (DMSO-d_6, 100.4 MHz)[c] 15.96 (q, C-18), 20.68 (q, CO$\underline{C}H_3$), 24.76 (t), 24.86 (t), 28.79 (t), 32.18 (t), 32.55 (t), 37.29 (d), 40.30 (d), 41.89 (d), 118.62 (d), 120.94 (d), 125.91 (d), 136.46 (s), 137.12 (s), 147.91 (s, C-3), 168.85 (s, $\underline{C}OCH_3$), 171.93 (s, C=O) and 178.71 (s, C=O); MS *m/z* (FAB+) 495.2 [10, $(M+H+NBA)^+$], 342.1 [100, $(M+H)^+$], 299.1 [40, $(M+H-Ac)^+$]; MS *m/z* (FAB-) 647.3 [12, $(M+2NBA)^-$], 493.2 [34, $(M-H+NBA)^-$], 340.1 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 342.17046, $C_{20}H_{24}NO_4$ requires 342.17053

[c]C-13 signal is hidden under the solvent peaks

Estrone 3-benzyl ether (8)

Sodium hydride (60% dispersion in mineral oil, 0.68 g, 20.34 mmol) was added to a stirred solution of E1 (5.0 g, 18.49 mmol) in anhydrous DMF (50 mL), at O^0C under an atmosphere of N_2. After stirring the resulting mixture for an additional 15 minutes, benzyl bromide (2.42 mL, 20.34 mmol) was added and the reaction mixture was heated at 80^0C for 4 hours. The excess of sodium hydride remaining was quenched by pouring the reaction mixture into ice/water. The organic fraction that separated was extracted into ethyl acetate (150 mL) and further washed exhaustively with water (4×50 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The pale yellow residue that obtained was recrystallized from isopropyl alcohol to give **8** as white flaky crystals (4.73 g, 71%): mp 129-131^0C (lit. 130-131°C)**ref**; TLC (chloroform/ethyl acetate, 4:1) R_f 0.83 cf. R_f 0.61 (E1); IR (KBr) 3100 (arom CH), 2950-2840 (aliph CH), 1730 (C=O), 1600, 1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.91 (3H, s, C-18-H_3), 1.41-2.54 (13H,m), 2.86-2.93 (2H, m, C-6-H_2), 5.04 (2H, s, OCH_2Ar), 6.73 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.80

(1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.20 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.30-7.44 (5H, m, C_6H_5).

3-Benzyl-marrianolic acid (9)

A solution of iodine (7.6 g, 29.94 mmol) in 95 mL of MeOH and a solution of KOH (13.7 g) in 27 mL of water and 61 mL of MeOH were added dropwise and alternatively to a stirred solution of estrone 3-benzyl ether (**8**) (3.8 g, 10.54 mmol) in MeOH (1 L) so that the colour of the mix remains orange/brown. The addition was carried out over 45 minutes and the resulting light yellow solution was stirred overnight at room temperature under an atmosphere of N_2 to give a clear light yellow solution. The mixture was then concentrated in vacuo and poured into water (800 mL). After acidification with 5M HCl, the organic fraction was extracted into ether (600 mL) and the ethereal layer washed with aqueous sodium thiosulfate (4×100 mL), then water (4×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The resulting yellow foam (4.54 g) was then dissolved in a solution of KOH (7.6 g) in MeOH/H_2O (1:2, 228 mL) and heated to reflux for 4 hours. The orange mixture that obtained was poured into water (800 mL) and after acidification with 5M HCl the organic fractions were extracted into ethyl acetate (300 mL). After further exhaustive washing with brine (4×200 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to give a yellow residue (4.32 g). This was recrystallized from $CHCl_3$/Hexane 5:3 to give **9** as a creamy powder (2.291 g, 53%). A further crop of the product (958 mg) was obtained from the residue of the mother liquor upon recrystallization from $CHCl_3$/Hexane 5:3 (overall yield 75%): mp 212-215^{0}C (lit. 226-227°C);[42] TLC (chloroform/methanol, 5:1) R_f 0.37 cf. R_f 0.88 (**8**); IR (KBr) 3050-2650 (CO_2H), 1700 (C=O), 1600-1500 (arom C=C) cm^{-1}; δ_H (DMSO-d_6, 400 MHz) 1.02 (3H, s, C-18-H_3), 1.20-2.78 (11H, m), 2.72-2.76 (2H, m, C-6-H_2), 5.05 (2H, s, OCH_2Ar), 6.68 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.75 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H), 7.18 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.9 Hz, C-1-H), 7.30-7.42 (5H, m, C_6H_5) and 12.14 (2H, s, exchanged with D_2O, CO_2H); δ_C (DMSO-d_6, 100.4 MHz) 15.37 (q, C-18), 25.84 (t), 26.53 (t), 29.73 (t), 35.77 (t), 36.10 (t), 40.73 (d), 41.84 (d), 42.55 (d), 46.21 (s, C-13), 68.93 (t, OCH_2Ar), 112.35 (d), 114.02 (d), 126.32 (d), 127.29 (2×d), 127.49 (d), 128.19 (2×d), 131.64 (s), 137.18 (2×s), 155.96 (s, C-3), 173.93 (s, CO_2H) and 178.60 (s,

CO_2H); MS *m/z* (FAB+) 408.2 [41, M^+], 91.1 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 408.19404, $C_{25}H_{28}O_5$ requires 408.19367.

3-Benzyloxy-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (10)

3-Benzyl-marrianolic acid (**9**) (3.25 g, 7.96 mmol) and urea (3.25 g, 54.11 mmol) were heated at 180^{0}C under an atmosphere of N_2 for 45 minutes. The resulting brown residue was then crushed and acetone was added (200 mL) to give a brown suspension. This mixture was concentrated to ca 100 mL, silica gel was added and the solvent was removed to give an homogeneous beige powder which was transferred onto a wet packed (chloroform) flash chromatography column. Elution with chloroform/acetone (96:4) gave **10** as a white residue (2.75 g, 89%): mp 225-226^{0}C; TLC (chloroform/acetone, 9:1) R_f 0.62 cf. R_f 0.14 (**9**); IR (KBr) 3260 (NH), 2900-2870 (aliph CH), 1720 (C=O), 1700 (C=O), 1600-1500 (arom C=C) cm^{-1}; δ_H (DMSO-d$_6$, 400 MHz) 1.09 (3H, s, C-18-H_3), 1.20-2.72 (11H, m), 2.76-2.80 (2H, m, C-6-H_2), 5.05 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.76 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.5 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.19 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 9.0 Hz, C-1-H), 7.31-7.44 (5H, m, C_6H_5) and 10.63 (1H, s, exchanged with D_2O, NH); δ_C (DMSO-d$_6$, 100.4 MHz) 16.16 (q, C-18), 25.06 (t), 25.25 (t), 29.25 (t), 32.37 (t), 32.72 (t), 37.82 (d), 40.32 (d), 40.49 (s), 41.91 (d), 68.89 (t, OCH_2Ar), 112.25 (d), 114.08 (d), 126.00 (d), 127.27 (2×d), 127.45 (d), 128.16 (2×d), 131.51 (s), 137.01 (s), 137.12 (s), 155.97 (s, C-3), 172.09 (s, C=O) and 178.89 (s, C=O); MS *m/z* (FAB+) 543.3 [8, $(M+H+NBA)^+$], 390.2 [58, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 390.20586, $C_{25}H_{28}NO_3$ requires 390.20692. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give colourless needles. HPLC (methanol/water, 85:15; λ_{max} = 278.1 nm) Rt = 8.15 min, 100%. Found: C, 76.90; H, 6.99; N, 3.73. $C_{25}H_{27}NO_3$ requires: C, 77.09; H, 6.99; N, 3.60.

VI – 2 – 2 – Introduction of various side chains on the D-ring *via N*-alkylations

3-Benzyloxy-*N*-methyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (11)

Following the alkylation conditions (see VI–1–3), **10** (500 mg, 1.28 mmol) was treated with NaH (62 mg, 1.54 mmol) and the subsequent reaction with methyl iodide (160 µL,

2.57 mmol) was complete within 45 minutes. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **11** as a white residue (432 mg, 83%): mp 118-121^{0}C; IR (KBr) 3160-3060 (arom CH), 2920-2870 (aliph CH), 1720 (C=O), 1670 (C=O), 1600-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.17 (3H, s, C-18-H_3), 1.26-3.00 (11H, m), 2.86-2.91 (2H, m, C-6-H_2), 3.15 (3H, s, N-CH_3), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.80 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.21 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.32-7.45 (5H, m, C_6H_5); δ_C ($CDCl_3$, 100.4 MHz) 16.64 (q, C-18), 25.58 (t), 25.83 (t), 26.98 (q, C-1'), 29.73 (t), 33.50 (t), 33.83 (t), 38.55 (d), 40.42 (d), 41.53 (s, C-13), 42.57 (d), 69.95 (t, OCH_2Ar), 112.56 (d), 114.51 (d), 126.14 (d), 126.29 (2×d), 127.75 (d), 128.42 (2×d), 131.49 (s), 137.01 (s), 137.16 (s), 156.82 (s, C-3), 171.81 (s, C=O) and 178.68 (s, C=O); MS *m/z* (FAB+) 404.4 [79, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 404.22174, $C_{26}H_{30}NO_3$ requires 404.22257. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give colourless crystals. HPLC (methanol/water, 90:10; λ_{max} = 278.1 nm) Rt = 3.93 min, 100%. Found: C, 77.30; H, 7.22; N, 3.48. $C_{26}H_{29}NO_3$ requires: C, 77.39; H, 7.24; N, 3.47.

3-Benzyloxy-*N*-ethyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (12)

Following the alkylation conditions (see VI–1–3), **10** (500 mg, 1.28 mmol) was treated with NaH (62 mg, 1.54 mmol) and the subsequent reaction with ethyl iodide (205 μL, 2.57 mmol) was complete within 1 hour. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **12** as a white residue (502 mg, 94%): mp 93-95°C; IR (KBr) 2975-2865 (aliph CH), 1715 (C=O), 1665 (C=O), 1605-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.11 (3H, t, *J* = 7.2 Hz, C-2'-H_3), 1.16 (3H, s, C-18-H_3), 1.31-2.98 (11H, m), 2.85-2.90 (2H, m, C-6-H_2), 3.81 (2H, m, N-CH_2), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.81 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.22 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.30-7.44 (5H, m, C_6H_5); δ_C ($CDCl_3$, 100.4 MHz) 13.15 (q, C-2'), 16.43 (q, C-18), 25.49 (t), 25.69 (t), 29.61 (t), 33.52 (t), 33.63 (t), 35.03 (t, C-1'), 38.54 (d), 40.22 (d), 41.28 (s, C-13), 42.42 (d), 69.84 (t, OCH_2Ar), 112.44 (d), 114.41 (d), 126.00 (d), 127.15 (2×d), 127.61 (d), 128.28 (2×d), 131.41 (s), 136.91 (s), 137.05 (s), 156.70 (s, C-3), 171.15 (s, C=O) and 178.03 (s, C=O); MS *m/z* (FAB+) 418.3 [90, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$];

Acc MS *m/z* (FAB+) 417.23061, $C_{27}H_{31}NO_3$ requires 417.23039. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give white crystals. **HPLC** (methanol/water, 85:15; λ_{max} = 278.1 nm) Rt = 8.15 min, 100%. **Found**: C,; H,; N,. $C_{27}H_{31}NO_3$ requires: C, 77.67; H, 7.48; N, 3.35.

3-Benzyloxy-*N*-propyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (13)

Following the alkylation conditions (see VI–1–3), **10** (500 mg, 1.28 mmol) was treated with NaH (62 mg, 1.54 mmol) and the subsequent reaction with propyl iodide (250 µL, 2.57 mmol) was complete within 2 hours. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **13** as a white residue (524 mg, 94%): mp 95-98^{0}C; IR (KBr) 3035 (arom CH), 2960-2870 (aliph CH), 1720 (C=O), 1660 (C=O), 1610-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.89 (3H, t, J = 7.6 Hz, C-3'-H_3), 1.16 (3H, s, C-18-H_3), 1.32-2.98 (13H, m), 2.83-2.88 (2H, m, C-6-H_2), 3.64-3.80 (2H, m, N-CH_2), 5.03 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.80 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.21 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.30-7.44 (5H, m, C_6H_5); δ_C ($CDCl_3$, 100.4 MHz) 11.44 (q, C-3'), 16.65 (q, C-18), 21.30 (t), 25.63 (t), 25.83 (t), 29.76 (t), 33.68 (t), 33.81 (t), 38.68 (d), 40.37 (d), 41.50 (s, C-13), 41.56 (t, C-1'), 42.54 (d), 69.97 (t, OCH_2Ar), 112.56 (d), 114.52 (d), 126.15 (d), 127.29 (2xd), 127.76 (d), 128.42 (2xd), 131.54 (s), 137.03 (s), 137.20 (s), 156.83 (s, C-3), 171.49 (s, C=O) and 178.43 (s, C=O); MS *m/z* (FAB+) 432.4 [88, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 432.25223, $C_{28}H_{34}NO_3$ requires 432.25387. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give white crystals. HPLC (methanol/water, 90:10; λ_{max} = 278.1 nm) Rt = 5.50 min, 100%. Found: C, 77.60; H, 7.68; N, 3.26. $C_{28}H_{33}NO_3$ requires: C, 77.93; H, 7.71; N, 3.25.

3-Benzyloxy-*N*-butyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (14)

Following the alkylation conditions (see VI–1–3), **10** (500 mg, 1.28 mmol) was treated with NaH (62 mg, 1.54 mmol) and the subsequent reaction with bromobutane (276 µL, 2.57 mmol) was complete within 4 hours. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **14** as a white residue (513 mg, 90%): mp 100-103^{0}C; IR (KBr) 2960-2870 (aliph CH), 1720 (C=O), 1665 (C=O), 1615-

1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.92 (3H, t, J = 7.2 Hz, C-4'-H_3), 1.16 (3H, s, C-18-H_3), 1.28-2.99 (15H, m), 2.84-2.89 (2H, m, C-6-H_2), 3.75 (2H, m, N-CH_2), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.81 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.22 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.29-7.45 (5H, m, C_6H_5); δ_C ($CDCl_3$, 100.4 MHz) 13.76 (q, C-4'), 16.48 (q, C-18), 20.15 (t), 25.49 (t), 25.69 (t), 29.60 (t), 30.01 (t), 33.54 (t), 33.67 (t), 38.54 (d), 39.75 (t, C-1'), 40.24 (d), 41.35 (s, C-13), 42.40 (d), 69.83 (t, OCH_2Ar), 112.42 (d), 114.40 (d), 126.00 (d), 127.14 (2×d), 127.60 (d), 128.28 (2×d), 131.41 (s), 136.90 (s), 137.05 (s), 156.69 (s, C-3), 171.30 (s, C=O) and 178.25 (s, C=O); MS *m/z* (FAB+) 446.3 [97, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 446.26912, $C_{29}H_{36}NO_3$ requires 446.26952. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give white needles. **HPLC** (methanol/water, 85:15; λ_{max} = 278.1 nm) Rt = 8.15 min, 100%. Found: C, 77.80; H, 7.89; N, 3.13. $C_{29}H_{35}NO_3$ requires: C, 78.17; H, 7.92; N, 3.14. **(slightly out)**

3-Benzyloxy-*N*-pentyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (15)

Following the alkylation conditions (see VI–1–3), **10** (500 mg, 1.28 mmol) was treated with NaH (62 mg, 1.54 mmol) and the subsequent reaction with pentyl bromide (318 µL, 2.57 mmol) was complete within 5 hours. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **15** as a white residue (550 mg, 93%): mp 104-107^{0}C; IR (KBr) 3100-3000 (arom CH), 2960-2870 (aliph CH), 1720 (C=O), 1660 (C=O), 1610-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.89 (3H, t, J = 7.2 Hz, C-5'-H_3), 1.16 (3H, s, C-18-H_3), 1.20-2.98 (17H, m), 2.83-2.89 (2H, m, C-6-H_2), 3.66-3.82 (2H, m, N-CH_2), 5.03 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.80 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.21 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.30-7.44 (5H, m, C_6H_5); δ_C ($CDCl_3$, 100.4 MHz) 14.10 (q, C-5'), 16.63 (q, C-18), 22.46 (t), 25.63 (t), 25.81 (t), 27.72 (t), 29.16 (t), 27.75 (t), 33.68 (t), 33.79 (t), 38.68 (d), 40.10 (t, C-1'), 40.35 (d), 41.48 (s, C-13), 42.54 (d), 69.96 (t, OCH_2Ar), 112.55 (d), 114.51 (d), 126.15 (d), 127.29 (2xd), 127.76 (d), 128.42 (2xd), 131.54 (s), 137.02 (s), 137.20 (s), 156.81 (s, C-3), 171.45 (s, C=O) and 178.39 (s, C=O); MS *m/z* (FAB+) 460.2 [78, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 460.28447, $C_{30}H_{38}NO_3$ requires 460.28517. For HPLC and CHN analysis, a sample was

recrystallized from EtOH to give colourless needles. HPLC (methanol/water, 92:8; λ_{max} = 276.9 nm) Rt = 6.46 min, 97.7%. Found: C, 78.20; H, 8.08; N, 3.01. $C_{30}H_{37}NO_3$ requires: C, 78.40; H, 8.11; N, 3.05.

3-Benzyloxy-*N*-hexyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (16)

Following the alkylation conditions (see VI–1–3), **10** (500 mg, 1.28 mmol) was treated with NaH (62 mg, 1.54 mmol) and the subsequent reaction with hexyl bromide (360 µL, 2.57 mmol) was complete within 1.5 hours. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **16** as a white residue (575 mg, 94%): mp 108-111^{0}C; IR (KBr) 2960-2860 (aliph CH), 1720 (C=O), 1665 (C=O), 1615-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.87 (3H, t, J = 6.6 Hz, C-6'-H_3), 1.16 (3H, s, C-18-H_3), 1.28-2.98 (19H, m), 2.84-2.89 (2H, m, C-6-H_2), 3.74 (2H, m, N-CH_2), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.81 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.22 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.29-7.44 (5H, m, C_6H_5); δ_C ($CDCl_3$, 100.4 MHz) 14.13 (q, C-6'), 16.63 (q, C-18), 22.63 (t), 25.64 (t), 25.84 (t), 26.69 (t), 27.99 (t), 29.76 (t), 31.56 (t), 33.69 (t), 33.82 (t), 38.70 (d), 40.14 (t, C-1'), 40.39 (d), 41.50 (s, C-13), 42.55 (d), 69.99 (t, OCH_2Ar), 112.58 (d), 114.55 (d), 126.15 (d), 127.29 (2×d), 127.76 (d), 128.42 (2×d), 131.57 (s), 137.05 (s), 137.20 (s), 156.84 (s, C-3), 171.44 (s, C=O) and 178.38 (s, C=O); MS *m/z* (FAB+) 474.3 [68, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 473.29238, $C_{31}H_{39}NO_3$ requires 473.29299. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give white needles. **HPLC** (methanol/water, 85:15; λ_{max} = 278.1 nm) Rt = 8.15 min, 100%. Found: C, 78.10; H, 8.16; N, 2.98. $C_{31}H_{39}NO_3$ requires: C, 78.61; H, 8.30; N, 2.96. **(slightly out)**

3-Benzyloxy-*N*-bromobutyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (17)

Following the alkylation conditions (see VI–1–3), **10** (500 mg, 1.28 mmol) was treated with NaH (62 mg, 1.54 mmol) and the subsequent reaction with 1,4-dibromobutane (310 µL, 2.57 mmol) was complete within 1.5 hours. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **17** as a white residue (569 mg, 84%): mp 113-116^{0}C; IR (KBr) 2935-2860 (aliph CH), 1720 (C=O), 1670 (C=O), 1605-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.17 (3H, s, C-18-H_3), 1.30-

3.00 (15H, m), 2.84-2.90 (2H, m, C-6-H_2), 3.42 (2H, t, J = 6.8 Hz, CH_2Br), 3.79 (2H, m, N-CH_2), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.81 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.21 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.30-7.45 (5H, m, C_6H_5); δ_C ($CDCl_3$, 100.4 MHz) 17.02 (q, C-18), 25.92 (t), 26.14 (t), 27.12 (t), 30.08 (t), 30.51 (t), 33.54 (t), 33.95 (t), 34.08 (t), 38.96 (d), 39.35 (t, C-1'), 40.62 (d), 41.85 (s, C-13), 42.85 (d), 70.27 (t, OCH_2Ar), 112.88 (d), 114.83 (d), 126.45 (d), 127.64 (2×d), 128.12 (d), 128.77 (2×d), 131.77 (s), 137.30 (s), 137.50 (s), 157.12 (s, C-3), 171.83 (s, C=O) and 178.76 (s, C=O); MS *m/z* (FAB+) 524.1 [42, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 525.17157, $C_{29}H_{34}{}^{81}BrNO_3$ requires 525.17016 and 524.17384, $C_{29}H_{34}BrNO_3$ requires 524.18003. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give white crystals. HPLC (methanol/water, 90:10; λ_{max} = 278.1 nm) Rt = 6.04 min, 99.7%. Found: C, 66.30; H, 6.51; N, 2.56. $C_{29}H_{34}BrNO_3$ requires: C, 66.41; H, 6.53; N, 2.67.

3-Benzyloxy-*N*-cyclopropylmethyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (18)

Following the alkylation conditions (see VI–1–3), **10** (500 mg, 1.28 mmol) was treated with NaH (62 mg, 1.54 mmol) and the subsequent reaction with bromomethyl-cyclopropane (246 μL, 2.57 mmol) was complete within 3 hours. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **18** as a white residue (536 mg, 94%): mp 96-99^{0}C; IR (KBr) 2920-2860 (aliph CH), 1720(C=O), 1670(C=O), 1610-1495 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.29-0.34 (2H, m, C-3'-H_2), 0.40-0.45 (2H, m, C-4'-H_2), 1.15 (1H, m, C-2'-H), 1.18 (3H, s, C-18-H_3), 1.25-3.01 (11H, m), 2.85-2.90 (2H, m, C-6-H_2), 3.67 (2H, m, N-CH_2), 5.04 (2H, s, OCH_2Ar), 6.73 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.81 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.22 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.29-7.45 (5H, m, C_6H_5); δ_C ($CDCl_3$, 100.4 MHz) 3.94 (t, C-3'), 4.02 (t, C-4'), 10.52 (d, C-2'), 16.96 (q, C-18), 25.96 (t), 26.15 (t), 30.08 (t), 34.03 (t), 34.14 (t), 39.06 (d), 40.65 (d), 41.86 (s, C-13), 42.86 (d), 44.59 (t, C-1'), 70.31 (t, OCH_2Ar), 112.90 (d), 114.87 (d), 126.45 (d), 127.60 (2×d), 128.06 (d), 128.73 (2×d), 131.91 (s), 137.37 (s), 137.52 (s), 157.16 (s, C-3), 171.99 (s, C=O) and 178.98 (s, C=O); MS *m/z* (FAB+) 887.3 [58, $(2M+H)^+$], 444.1 [98, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 443.24533, $C_{29}H_{33}NO_3$ requires 443.24604. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give

white needles. **HPLC** (methanol/water, 85:15; λ_{max} = 278.1 nm) Rt = 8.15 min, 100%. Found: C, 78.30; H, 7.47; N, 3.18. $C_{29}H_{33}NO_3$ requires: C, 78.52; H, 7.50; N, 3.16.

3-Benzyloxy-*N*-(3-picolyl)-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (19)

Sodium hydride (60% dispersion in mineral oil, 31 mg, 770 μmol) was added to a stirred solution of **10** (250 mg, 642 μmol) in anhydrous DMF (10 mL) at room temperature under an atmosphere of N_2. After evolution of hydrogen had ceased, 3-(Bromomethyl)pyridine hydrobromide (325 mg, 1.28 mmol) was added to give a deep orange mixture. This was stirred for 2 hours at room temperature, then an additional 2 equivalents of sodium hydride (52 mg, 1.28 mmol) were added to the mixture. This was stirred overnight at room temperature and poured into water (40 mL). The resulting dark red mixture was extracted into ethyl acetate (40 mL). After further exhaustive washing with brine (4×20 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo. Fractionation of the crude product that obtained by flash chromatography with chloroform/acetone (9:1) as eluent gave **19** as a white residue which was further purified by a second flash column with chloroform/acetone (95:5). A white powder was obtained (230 mg, 75%): mp 170-172^{0}C; IR (KBr) 2925-2870 (aliph CH), 1720 (C=O), 1670 (C=O), 1610-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.14 (3H, s, C-18-H_3), 1.28-3.04 (11H, m), 2.84-2.88 (2H, m, C-6-H_2), 4.92 (1H, d, J_{BA}= 13.7 Hz, N-C$\underline{H_A}$$H_B$Py), 4.98 (1H, d, J_{AB} = 14.1 Hz, N-C$H_A$$\underline{H_B}$Py), 5.03 (2H, s, OCH_2Ar), 6.71 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.79 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.17-7.45 (7H, m, C_6H_5, C-1-H and C-4''-H), 7.69 (1H, td, $J_{C\text{-}4''\text{-}H,\ C\text{-}3''\text{-}H}$ = 7.8 Hz, $J_{C\text{-}5''\text{-}H,\ C\text{-}3''\text{-}H}$ = $J_{C\text{-}1''\text{-}H,\ C\text{-}3''\text{-}H}$ = 1.9 Hz, C-2''-H), 8.50 (1H, dd, $J_{C\text{-}4''\text{-}H,\ C\text{-}5''\text{-}H}$ = 5.1 Hz, $J_{C\text{-}3''\text{-}H,\ C\text{-}5''\text{-}H}$ = 1.6 Hz, C-5''-H) and 8.63 (1H, d, $J_{C\text{-}3''\text{-}H,\ C\text{-}1''\text{-}H}$ = 1.9 Hz, C-1''-H); δ_C ($CDCl_3$, 100.4 MHz) 16.49 (q, C-18), 25.51 (t), 25.77 (t), 29.68 (t), 33.56 (t), 33.66 (t), 38.52 (d), 40.14 (d), 40.85 (t, C-1'), 41.58 (s, C-13), 42.43 (d), 69.93 (t, -OCH_2Ar), 112.55 (d), 114.47 (d), 123.19 (d), 126.12 (d), 127.26 (2×d), 127.75 (d), 128.41 (2×d), 131.35 (s), 132.80 (s), 136.37 (d), 137.10 (2×s), 148.59 (d), 150.03 (d), 156.80 (s, C-3), 171.36 (s, C=O) and 178.31 (s, C=O); MS *m/z* (FAB+) 481.3 [100, $(M+H)^+$], 91.1 [47, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 481.25036, $C_{31}H_{33}N_2O_3$ requires 481.24912. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give colourless needles. HPLC (methanol/water,

90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. Found: C, 77.00; H, 6.75; N, 5.73. $C_{32}H_{33}N_2O_3$ requires: C, 77.47; H, 6.71; N, 5.83.

3-Benzyloxy-*N*-*tert*-butyl-benzyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (20)

Following the alkylation conditions (see VI–1–3), **10** (500 mg, 1.28 mmol) was treated with NaH (62 mg, 1.54 mmol) and the subsequent reaction with 1-bromomethyl-4-*tert*-butyl-benzene (472 μL, 2.57 mmol) was complete within 30 minutes. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **20** as a white residue (667 mg, 97%): mp 199-200^{0}C; IR (KBr) 2965-2870 (aliph CH), 1720 (C=O), 1670(C=O), 1605-1505 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.16 (3H, s, C-18-H_3), 1.28 (9H, s, $C(CH_3)_3$), 1.30-3.01 (11H, m), 2.84-2.90 (2H, m, C-6-H_2), 4.88 (1H, d, J_{BA} = 13.7 Hz, N-C$\underline{H_A}$$CH_B$), 4.94 (1H, d, J_{AB} = 14.1 Hz, N-CH_AC$\underline{H_B}$), 5.03 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.80 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.21 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.24-7.44 (9H, m, C_6H_5, C-2''-H, C-3''-H, C-5''-H and C-6''-H); δ_C ($CDCl_3$, 100 .4 MHz) 16.60 (q, C-18), 25.60 (t), 25.79 (t), 29.73 (t), 31.40 (3×q, C($\underline{C}H_3)_3$), 33.67 (t), 33.77 (t), 34.53 (s, $\underline{C}(CH_3)_3$), 38.63 (d), 40.15 (d), 41.55 (s, C-13), 42.48 (d), 42.88 (t, C-1'), 69.93 (t, OCH_2Ar), 112.53 (d), 114.47 (d), 125.20 (2×d), 126.15 (d), 127.30 (2×d), 127.77 (d), 128.02 (2×d), 128.42 (2×d), 131.48 (s), 134.20 (s), 136.98 (s), 137.17 (s), 149.91 (s), 156.79 (s, C-3), 171.42 (s, C=O) and 178.37 (s, C=O); MS *m/z* (FAB+) 1071.5 [32, $(2M+H)^+$], 536.2 [80, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]; MS *m/z* (FAB-) 534.3 [72, $(M-H)^-$], 195.0 [100], 276.0 [100] Acc MS *m/z* (FAB+) 535.30865, $C_{36}H_{41}NO_3$ requires 535.30864. For HPLC and CHN analysis, a sample was recrystallized from EtOH to give white needles. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. **Found:** C,; H,; N,. $C_{29}H_{35}NO_3$ requires: C, 80.71; H, 7.71; N, 2.61.

3-Benzyloxy-*N*-benzyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (21)

3-Benzyl-marrianolic acid (**9**) (500 mg, 1.22 mmol) was stirred with benzylamine (6.25 mL, 57.22 mmol) and heated at 180°C under an atmosphere of N_2 for 3 hours. After cooling down, the resulting brown mixture was poured into water (250 mL), acidified with HCl 5M, and the organic fractions were extracted into ethyl acetate (50 mL). After further exhaustive washing with water (1×25 mL), then brine (3×25 mL), the organic

layer was dried ($MgSO_4$), filtered and evaporated in vacuo. Fractionation of the crude product that obtained by flash chromatography with chloroform/hexane (8/2) as eluent gave **21** as a creamy powder (385 mg, 65%): mp 144-146^{0}C; IR (KBr) 3100 (arom CH), 2940-2850 (aliph CH), 1720 (C=O), 1670 (C=O), 1615-1560 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.15 (3H, s, C-18-H_3), 1.25-3.01 (11H, m), 2.84-2.89 (2H, m, C-6-H_2), 4.91 (1H, d, J_{BA} = 13.7 Hz, N-C$\underline{H_A}H_B$Ar), 4.98 (1H, d, J_{AB} = 13.7 Hz, N-C$H_A\underline{H_B}$Ar), 5.03 (2H, s, OCH_2Ar), 6.72 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.80 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.21 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.2 Hz, C-1-H) and 7.24-7.43 (10H, m, 2×C_6H_5); δ_C ($CDCl_3$, 100.4 MHz) 16.54 (q, C-18), 25.59 (t), 25.80 (t), 29.73 (t), 33.66 (t), 33.75 (t), 38.64 (d), 40.17 (d), 41.54 (s, C-13), 42.48 (d), 43.22 (t, C-1'), 69.93 (t, OCH_2Ar), 112.54 (d), 114.48 (d), 126.14 (d), 127.19 (d), 127.29 (d), 127.76 (d), 128.27 (d), 128.39 (d), 128.42 (d), 131.47 (s), 136.98 (s), 137.16 (s), 137.25 (s), 156.80 (s, C-3), 171.39 (s, C=O) and 178.31 (s, C=O); MS *m/z* (FAB+) 480.2 [52, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]; Acc MS *m/z* (FAB+) 480.25223, $C_{32}H_{34}NO_3$ requires 480.25387. For HPLC and CHN analysis, a sample was recrystallized from MeOH to give colourless needles. HPLC (methanol/water, 90:10; λ_{max} = 220.0 nm) Rt = 5.83 min, 99.0%. Found: C, 80.10; H, 6.91; N, 2.94. $C_{32}H_{33}NO_3$ requires: C, 80.14; H, 6.94; N, 2.92.

V – 2 – 3 – Deprotection of the precursors

3-Hydroxy-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (5)

Following the hydrogenation conditions (see VI-1-4), a suspension of **10** (350 mg, 899 μmol) and Pd-C (10%, 100 mg) in MeOH/THF 1:1 (50 mL) was hydrogenated for 5 hours to give **5** as a white solid (246 mg, 91%). An analytical sample was recrystallized from $CHCl_3$/Hexane 2:1 to give white crystals: mp 297-300^{0}C; TLC (chloroform/acetone, 8:2) R_f 0.39 cf. R_f 0.58 (**10**); IR (KBr) 3410 (OH), 3180-3085 (arom CH), 2955-2870 (aliph CH), 1715 (C=O), 1680 (C=O), 1615-1500 (arom C=C) cm^{-1}; δ_H (DMSO-d_6, 400 MHz) 1.09 (3H, s, C-18-H_3), 1.15-2.66 (11H, m), 2.69-2.73 (2H, m, C-6-H_2), 6.44 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.52 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.07 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H), 9.05 (1H, s, exchanged with D_2O, OH) and 10.63 (1H, s, exchanged with D_2O, NH); δ_C (DMSO-d_6, 100.4 MHz) 16.21 (q, C-18),

25.17 (t), 25.38 (t), 29.19 (t), 32.40 (t), 32.77 (t), 38.00 (d), 40.36 (d), 40.53 (s, C-13), 41.45 (d), 112.74 (d), 114.51 (d), 125.88 (d), 129.48 (s), 136.71 (s), 154.81 (s, C-3), 172.16 (s, C=O) and 178.97 (s, C=O); MS *m/z* (FAB+) 453.1[17, $(M+H+NBA)^+$], 300.0 [100, $(M+H)^+$], 213.1 [16], 159.1 [20], 133.0 [29], 111.1 [36], 97.1 [60]; MS *m/z* (FAB-) 605.4 [20, $(M+2NBA)^-$], 451.3 [58, $(M-H+NBA)^-$], 298.2 [100, $(M-H)^-$], 276.1 [21], 188.1 [25], 139.1 [19]; Acc MS *m/z* (FAB+) 300.15853, $C_{18}H_{22}NO_3$ requires 300.15997. HPLC (methanol/water, 60:40; λ_{max} = 279.3 nm) Rt = 3.06 min, 100%. Found: C, 61.80; H, 5.85; N, 3.86. $C_{18}H_{21}NO_3 + (CHCl_3)_{1/2}$ requires: C, 61.88; H, 6.04; N, 3.90.

3-Hydroxy-*N*-methyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (20)

Following the hydrogenation conditions (see VI-1-4), a suspension of **11** (400 mg, 992 μmol) and Pd-C (10%, 200 mg) in MeOH/THF 2:1 (30 mL) was hydrogenated for 2 hours to give **22** as a white solid (253 mg, 81%). An analytical sample was recrystallized from ethyl acetate to give white crystals: mp 328-330^{0}C; IR (KBr) 3460 (OH), 2940-2860 (aliph CH), 1715 (C=O), 1655 (C=O), 1610-1510 (arom C=C) cm^{-1}; δ_H (DMSO-d$_6$, 400 MHz) 1.09 (3H, s, C-18-H_3), 1.19-2.97 (11H, m), 2.68-2.73 (2H, m, C-6-H_2), 2.98 (3H, s, N-CH_3), 6.44 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.52 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H), 7.06 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 9.05 (1H, s, exchanged with D_2O, OH); δ_C (DMSO-d$_6$, 100.4 MHz)[a] 16.32 (q, C-18), 25.19 (t), 26.37 (q, C-1'), 29.11 (t), 32.78 (t), 33.55 (2×t), 37.83 (d), 40.90 (d), 41.86 (d), 112.71 (d), 114.50 (d), 125.81 (d), 129.40 (s), 136.68 (s), 154.80 (s, C-3), 171.35 (s, C=O) and 178.24 (s, C=O); MS *m/z* (FAB+) 314.1 [78, $(M+H)^+$], 97.1 [100]; Acc MS *m/z* (FAB+) 314.17487, $C_{19}H_{24}NO_3$ requires 314.17562. HPLC (methanol/water, 70:30; λ_{max} = 279.3 nm) Rt = 3.24 min, 100%. Found: C, 72.60; H, 7.16; N, 4.35. $C_{19}H_{23}NO_3$ requires: C, 72.82; H, 7.40; N, 4.47.

[a]C-13 signal is hidden under the solvent peaks

3-Hydroxy-*N*-ethyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (23)

Following the hydrogenation conditions (see VI-1-5), a suspension of **12** (470 mg, 1.13 mmol) and Pd-C (10%, 200 mg) in MeOH/THF 2:1 (30 mL) was hydrogenated for 4.5 hours to give **23** as a white solid (183 mg, 50%).This was washed in acetone to give a white powder (121 mg, 33%): mp 306-308^{0}C; IR (KBr) 3450 (OH), 2915-2860 (aliph

CH), 1715 (C=O), 1655 (C=O), 1610-1505 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.11 (3H, t, J = 7.0 Hz, C-2'-H_3), 1.16 (3H, s, C-18-H_3), 1.22-2.98 (11H, m), 2.81-2.87 (2H, m, C-6-H_2), 3.82 (2H, m, N-CH_2), 4.62 (1H, s, exchanged with D_2O, OH), 6.57 (1H, d, $J_{C-2-H,C-4-H}$ = 2.7 Hz, C-4-H), 6.66 (1H, dd, $J_{C-1-H,C-2-H}$ = 8.6 Hz and $J_{C-4-H,C-2-H}$ = 2.7 Hz, C-2-H) and 7.17 (1H, d, $J_{C-2-H,C-1-H}$ = 8.6 Hz, C-1-H); MS *m/z* (FAB+) 328.2 [100, $(M+H)^+$], 481.2 [13, $(M+H+NBA)^+$]; Acc MS *m/z* (FAB+) 328.19062, $C_{20}H_{26}NO_3$ requires 328.19127. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. Found: C, 72.90; H, 7.68; N, 4.09. $C_{20}H_{25}NO_3$ requires: C, 73.37; H, 7.70; N, 4.28. **(slightly out)**

3-Hydroxy-*N*-propyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (24)

Following the hydrogenation conditions (see VI-1-5), a suspension of **13** (400 mg, 927 μmol) and Pd-C (10%, 100 mg) in MeOH/THF 2:1 (30 mL) was hydrogenated for 3 hours to give **24** as a white solid (256 mg, 81%). An analytical sample was recrystallized from methanol to give colourless crystals: mp 183-186^{0}C; IR (KBr) 3445 (OH), 3050 (arom CH), 2940-2860 (aliph CH), 1725 (C=O), 1655 (C=O), 1585-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.90 (3H, t, J = 7.4 Hz, C-3'-H_3), 1.17 (3H, s, C-18-H_3), 1.30-2.98 (13H, m), 2.82-2.86 (2H, m, C-6-H_2), 3.64-3.80 (2H, m, N-CH_2), 4.73 (1H, s, exchanged with D_2O, OH), 6.58 (1H, d, $J_{C-2-H,C-4-H}$ = 2.7 Hz, C-4-H), 6.66 (1H, dd, $J_{C-1-H,C-2-H}$ = 8.6 Hz and $J_{C-4-H,C-2-H}$ = 2.7 Hz, C-2-H) and 7.17 (1H, d, $J_{C-2-H,C-1-H}$ = 8.6 Hz, C-1-H); δ_C ($CDCl_3$, 100.4 MHz) 11.43 (q, C-3'), 16.64 (q, C-18), 21.29 (t), 25.62 (d), 25.76 (t), 29.56 (t), 33.65 (t), 33.75 (t), 38.66 (d), 40.32 (d), 41.51 (s, C-13), 41.63 (t, C-1'), 42.48 (d), 112.97 (d), 114.98 (d), 126.30 (d), 131.15 (s), 137.39 (s), 153.66 (s, C-3), 171.76 (s, C=O) and 178.59 (s, C=O); MS *m/z* (FAB+) 342.3 [100, $(M+H)^+$], 133.2 [17], 111.2 [23], 97.2 [45]; MS *m/z* (FAB-) 494.4 [43, $(M+NBA)^-$], 340.3 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 342.20756, $C_{21}H_{28}NO_3$ requires 342.20692. HPLC (methanol/water, 70:30; λ_{max} = 279.3 nm) Rt = 6.55 min, 100%. Found: C, 73.90; H, 7.98; N, 4.20. $C_{21}H_{27}NO_3$ requires: C, 73.87; H, 7.97; N, 4.10.

3-Hydroxy-*N*-butyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (25)

Following the hydrogenation conditions (see VI-1-5), a suspension of **14** (480 mg, 1.08 mmol) and Pd-C (10%, 200 mg) in MeOH/THF 2:1 (30 mL) was hydrogenated for 2

hours to give **25** as a white solid (361 mg, 94%). This was recrystallized from methanol to give colourless needles (193 mg, 50%) and a further crop of the product (49 mg) was obtained from the residue of the mother liquor upon recrystallization from methanol (overall yield 63%): mp 212-214^{0}C; IR (KBr) 3445 (OH), 2940-2870 (aliph CH), 1715 (C=O), 1655 (C=O), 1585-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.92 (3H, m, C-4'-H_3), 1.16 (3H, s, C-18-H_3), 1.26-2.99 (15H, m), 2.81-2.88 (2H, m, C-6-H_2), 3.75 (2H, m, N-CH_2), 4.75 (1H, s, exchanged with D_2O, OH), 6.58 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.66 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.17 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); δ_C ($CDCl_3$, 100.4 MHz) 13.76 (q, C-4'), 16.49 (q, C-18), 20.15 (t), 25.51 (t), 25.66 (t), 29.43 (t), 30.01 (t), 33.54 (t), 33.66 (t), 38.57 (d), 39.83 (t, C-1'), 40.24 (d), 41.39 (s, C-13), 42.37 (d), 112.86 (d), 114.86 (d), 126.16 (d), 131.08 (s), 137.26 (s), 153.54 (s, C-3), 171.54 (s, C=O) and 178.40 (s, C=O); MS *m/z* (FAB+) 509.3 [5, $(M+H+NBA)^+$], 356.2 [100, $(M+H)^+$]; MS *m/z* (FAB-) 508.2 [35, $(M+NBA)^-$], 354.2 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 356.22247, $C_{22}H_{30}NO_3$ requires 356.22257. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. Found: C, 74.20; H, 8.21; N, 3.88. $C_{22}H_{29}NO_3$ requires: C, 74.33; H, 8.22; N, 3.94.

3-Hydroxy-*N*-pentyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (26)

Following the hydrogenation conditions (see VI-1-5), a suspension of **15** (520 mg, 1.13 mmol) and Pd-C (10%, 100 mg) in MeOH/THF 2:1 (30 mL) was hydrogenated for 3 hours to give **26** as a white solid (347 mg, 83%). An analytical sample was recrystallized from methanol to give white crystals: mp 181-184^{0}C; IR (KBr) 3445 (OH), 2955-2870 (aliph CH), 1715 (C=O), 1660 (C=O), 1610-1505 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.89 (3H, t, J = 7.4 Hz, C-5'-H_3), 1.16 (3H, s, C-18-H_3), 1.20-2.98 (17H, m), 2.81-2.86 (2H, m, C-6-H_2), 3.65-3.82 (2H, m, N-CH_2), 4.77-4.79 (1H, m, exchanged with D_2O, OH), 6.58 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.65 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.2 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.17 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.2 Hz, C-1-H); δ_C ($CDCl_3$, 100.4 MHz) 14.10 (q, C-5'), 16.63 (q, C-18), 22.46 (t), 25.64 (t), 25.77 (t), 27.71 (t), 29.15 (t), 29.75 (t), 33.66 (t), 33.76 (t), 38.67 (d), 40.16 (t, C-1'), 40.32 (d), 41.50 (s, C-13), 42.49 (d), 112.97 (d), 114.98 (d), 126.31 (d), 131.19 (s), 137.40 (s), 153.65 (s, C-3), 171.67 (s, C=O) and 178.52 (s, C=O); MS *m/z* (FAB+) 739.1 [50, $(2M+H)^+$], 523.0 [20,

(M+H+NBA)$^+$], 370.1 [100, (M+H)$^+$], 97.0 [15]; MS *m/z* (FAB-) 737.6 [20, (2M-H)$^-$], 675.4 [8, (M+2NBA)$^-$], 522.4 [30, (M+NBA)$^-$], 368.3 [100, (M-H)$^-$]; Acc MS *m/z* (FAB+) 370.23940, $C_{23}H_{32}NO_3$ requires 370.23822. HPLC (methanol/water, 80:20; λ_{max} = 279.3 nm) Rt = 5.42 min, 100%. Found: C, 74.90; H, 8.38; N, 3.73. $C_{23}H_{31}NO_3$ requires: C, 74.96; H, 8.46; N, 3.79.

3-Hydroxy-*N*-hexyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (27)

Following the hydrogenation conditions (see VI-1-5), a suspension of **16** (540 mg, 1.14 mmol) and Pd-C (10%, 200 mg) in MeOH/THF 2:1 (45 mL) was hydrogenated for 3 hours to give **27** as a white solid (384 mg, 88%). This was recrystallized from methanol to give white crystals (218 mg, 50%) and a further crop of the product (45 mg) was obtained from the residue of the mother liquor upon recrystallization from methanol (overall yield 60%): mp 157-159^{0}C; IR (KBr) 3435 (OH), 2930-2865 (aliph CH), 1715 (C=O), 1660 (C=O), 1585-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.87 (3H, t, J = 6.8 Hz, C-6'-H_3), 1.16 (3H, s, C-18-H_3), 1.23-2.98 (19H, m), 2.81-2.87 (2H, m, C-6-H_2), 3.74 (2H, m, N-CH_2), 4.68 (1H, s, exchanged with D_2O, OH), 6.58 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.66 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.2 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.17 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); δ_C ($CDCl_3$, 100.4 MHz) 14.00 (q, C-6'), 16.48 (q, C-18), 22.48 (t), 25.46 (t), 25.59 (t), 26.53 (t), 27.82 (t), 29.41 (t), 31.39 (t), 33.49 (t), 33.58 (t), 38.48 (d), 40.06 (t, C-1'), 40.12 (d), 41.33 (s, C-13), 42.31 (d), 112.81 (d), 114.82 (d), 126.16 (d), 130.98 (s), 137.23 (s), 153.48 (s, C-3), 171.58 (s, C=O) and 178.40 (s, C=O); MS *m/z* (FAB+) 767.6 [48, (2M+H)$^+$], 384.3 [100, (M+H)$^+$]; MS *m/z* (FAB-) 765.5 [8, (2M-H)$^-$], 536.3 [10, (M+NBA)$^-$], 382.2 [100, (M-H)$^-$]; Acc MS *m/z* (FAB+) 384.25350, $C_{24}H_{34}NO_3$ requires 384.25387. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. Found: C, 75.40; H, 8.65; N, 3.71. $C_{24}H_{33}NO_3$ requires: C, 75.16; H, 8.67; N, 3.65.

3-Hydroxy-*N*-bromobutyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (28)

Following the hydrogenation conditions (see VI-1-5), a suspension of **17** (210 mg, 381 μmol) and Pd-C (10%, 100 mg) in MeOH/THF 2:1 (30 mL) was hydrogenated for 2 hours to give **28** as a white solid (146 mg, 84%). This was recrystallized from methanol to give white crystals (98 mg, 57%): mp 165-167^{0}C; IR (KBr) 3450 (OH), 2910-2860 (aliph CH), 1715 (C=O), 1660 (C=O), 1610-1505 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.18

(3H, s, C-18-H_3), 1.29-3.01 (15H, m), 2.82-2.88 (2H, m, C-6-H_2), 3.42 (2H, t, J = 6.6 Hz, CH_2Br), 3.72-3.87 (2H, m, N-CH_2), 4.63 (1H, s, exchanged with D_2O, OH), 6.58 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.66 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H) and 7.17 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); δ_C (DMSO-d_6, 100.4 MHz) 17.01 (q, C-18), 25.92 (t), 26.09 (t), 27.11 (t), 29.87 (t), 30.51 (t), 33.47 (t), 33.94 (t), 34.06 (t), 38.96 (d), 39.38 (t, C-1'), 40.62 (d), 41.86 (s, C-13), 42.80 (d), 113.29 (d), 115.28 (d), 126.62 (d), 131.53 (s), 137.73 (s), 153.87 (s, C-3), 171.93 (s, C=O) and 178.81 (s, C=O); MS *m/z* (FAB+) 869.2 [64], 587.1 [46, $(M+H+NBA)^+$], 434.1 [100, $(M+H)^+$]; Acc MS *m/z* (FAB+) 436.12874, $C_{22}H_{29}{}^{81}BrNO_3$ requires 436.13103 and 434.12822, $C_{22}H_{29}BrNO_3$ requires 434.13308. HPLC (methanol/water, 70:30; λ_{max} = 279.3 nm) Rt = 7.73 min, 98.3%. Found: C, 61.30; H, 6.60; N, 3.17. $C_{22}H_{28}BrNO_3$ requires: C, 60.83; H, 6.50; N, 3.22.

3-Hydroxy-*N*-cyclopropylmethyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (29)

Following the hydrogenation conditions (see VI-1-5), a suspension of **18** (500 mg, 1.13 mmol) and Pd-C (10%, 200 mg) in MeOH/THF 2:1 (45 mL) was hydrogenated for 2.5 hours to give **29** as a white solid (356 mg, 89%). This was recrystallized from methanol to give colourless crystals (181 mg, 45%) and a further crop of the product (73 mg) was obtained from the residue of the mother liquor upon recrystallization from methanol (overall yield 64%): mp 238-240^{0}C; IR (KBr) 3440 (OH), 2940-2865 (aliph CH), 1715 (C=O), 1655 (C=O), 1610-1505 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.29-0.34 (2H, m, C-3'-H_2), 0.40-0.45 (2H, m, C-4'-H_2), 1.13 (1H, m, C-2'-H), 1.19 (3H, s, C-18-H_3), 1.30-3.02 (11H, m), 2.82-2.89 (2H, m, C-6-H_2), 3.66 (2H, m, N-CH_2), 4.70 (1H, s, exchanged with D_2O, OH), 6.58 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.66 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.2 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.17 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); δ_C ($CDCl_3$, 100.4 MHz) 3.95 (t, C-3'), 4.03 (t, C-4'), 10.51 (d, C-2'), 16.95 (q, C-18), 25.97 (t), 26.10 (t), 29.88 (t), 31.10 (t), 34.00 (t), 39.05 (d), 40.62 (d), 41.88 (s, C-13), 42.81 (d), 44.65 (t, C-1'), 113.30 (d), 115.31 (d), 126.61 (d), 131.56 (s), 137.73 (s), 153.96 (s, C-3), 172.21 (s, C=O) and 179.10 (s, C=O); MS *m/z* (FAB+) 707.3 [29, $(2M+H)^+$], 507.1 [72, $(M+H+NBA)^+$], 354.1 [100, $(M+H)^+$]; MS *m/z* (FAB-) 658.3 [13, $(M-H+2NBA)^-$], 505.2 [32, $(M-H+NBA)^-$], 352.1 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 354.20686, $C_{22}H_{28}NO_3$ requires 354.20692. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2

nm) Rt = 3.90 min, 100%. **Found:** C,; H,; N,. $C_{22}H_{27}NO_3$ requires: C, 74.76; H, 7.70; N, 3.96.

3-Hydroxy-*N*-(3-picolyl)-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (30)

Following the hydrogenation conditions (see VI-1-5), a suspension of **19** (190 mg, 395 μmol) and Pd-C (10%, 100 mg) in MeOH/THF 2:1 (30 mL) was hydrogenated for 20 hours to give **30** as a creamy solid (141 mg, 91%). An analytical sample was precipitated from ethyl acetate to give a white powder: **mp**; IR (KBr) 3380 (OH), 2940-2865 (aliph CH), 1720 (C=O), 1670 (C=O), 1610-1500 (arom C=C) cm^{-1}; δ_H (DMSO-d_6, 400 MHz) 1.11 (3H, s, C-18-H_3), 1.14-2.94 (11H, m), 2.67-2.75 (2H, m, C-6-H_2), 4.82 (1H, d, J_{BA} = 14.8 Hz, N-C$\underline{H_A}$$H_B$), 4.87 (1H, d, J_{AB} = 14.8 Hz, N-C$H_A$$\underline{H_B}$), 6.44 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.52 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H), 7.07 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H), 7.33 (1H, dd, $J_{C\text{-}3''\text{-}H,\ C\text{-}4''\text{-}H}$ = 7.8 Hz, $J_{C\text{-}5''\text{-}H,\ C\text{-}4''\text{-}H}$ = 4.7 Hz, C-4''-H), 7.59 (1H, m, C-3''-H), 8.42-8.47 (2H, m, C-1''-H and C-5''-H) and 9.05 (1H, s, exchanged with D_2O, OH); MS *m/z* (FAB+) 544.3 [6, $(M+H+NBA)^+$], 391.2 [88, $(M+H)^+$], 273.1 [18], 156.1 [40], 135.1 [46], 119.1 [48], 95.1 [70]; MS *m/z* (FAB-) 542.3 [50, $(M-H+NBA)^-$], 389.3 [100, $(M-H)^-$], 276.1 [43], 258.1 [37], 195.1 [42], 124.1 [34], 92.0 [27] Acc MS *m/z* (FAB+) 391.20190, $C_{24}H_{27}N_2O_3$ requires 391.20217.

3-Hydroxy-*N*-*tert*-butyl-benzyl -16,17-seco-estra-1,3,5(10)-triene-16,17-imide (31)

Following the hydrogenation conditions (see VI-1-5), a suspension of **20** (620 mg, 1.16 mmol) and Pd-C (10%, 200 mg) in MeOH/THF 2:1 (30 mL) was hydrogenated for 5 hours to give **31** as a creamy solid (550 mg). This was recrystallized from methanol to give white flaky crystals (417 mg, 81%) and a further crop of the product (31 mg) was obtained from the residue of the mother liquor upon recrystallization from methanol (overall yield 87%): mp 128-130^{0}C; IR (KBr) 3415 (OH), 2955-2870 (aliph CH), 1725 (C=O), 1655 (C=O), 1610-1505 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.16 (3H, s, C-18-H_3), 1.28 (9H, s, $C(CH_3)_3$), 1.30-3.02 (15H, m), 2.81-2.87 (2H, m, C-6-H_2), 4.77 (1H, s, exchanged with D_2O, OH), 4.88 (1H, d, J_{BA} = 14.0 Hz, N-C$\underline{H_A}$$H_B$), 4.95 (1H, d, , J_{AB} = 14.0 Hz, N-C$H_A$$\underline{H_B}$), 6.57 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.65 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.2 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.16 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.24-7.32 (4H, m, C-2''-H, C-3''-H, C-5''-H and C-6''-H); δ_C ($CDCl_3$, 100.4 MHz)

16.93 (q, C-18), 25.94 (t), 26.07 (t), 29.88 (t), 31.74 (3×q, C(<u>C</u>H$_3$)$_3$), 33.99 (t), 34.07 (t), 34.87 (s, <u>C</u>(CH$_3$)$_3$), 38.96 (d), 40.44 (d), 41.90 (s, C-13), 42.76 (d), 43.27 (t, C-1'), 113.30 (d), 115.30 (d), 125.55 (2×d), 126.64 (d), 128.35 (2×d), 131.45 (s), 134.44 (s), 137.71 (s), 150.30 (s), 153.95 (s, C-3), 172.01 (s, C=O) and 178.85 (s, C=O); MS *m/z* (FAB+) 891.4 [80, $(2M+H)^+$], 599.2 [35, $(M+H+NBA)^+$], 446.2 [100, $(M+H)^+$]; MS *m/z* (FAB-) 889.5 [42, $(2M-H)^-$], 751.4 [87, $(M+2NBA)^-$], 598.3 [30, $(M+NBA)^-$], 444.2 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 445.26176, $C_{29}H_{35}NO_3$ requires 354.20692. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. **Found:** C,; H,; N,. $C_{22}H_{27}NO_3$ requires: C, 74.76; H, 7.70; N, 3.96.

3-Hydroxy-*N*-benzyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (32)

Following the hydrogenation conditions (see VI-1-5), a suspension of **21** (230 mg, 479 μmol) and Pd-C (10%, 100 mg) in MeOH/THF 2:1 (30 mL) was hydrogenated for 2 hours to give **32** as a white solid (170 mg, 91%). This was washed with boiling MeOH to give a white precipitate (122 mg, 65%) : mp 298-301^{0}C; IR (KBr) 3430 (OH), 2950-2890 (aliph CH), 1720 (C=O), 1655 (C=O), 1610-1505 (arom C=C) cm^{-1}; δ_H (DMSO-d$_6$, 400 MHz) 1.12 (3H, s, C-18-H$_3$), 1.18-2.92 (11H, m), 2.68-2.75 (2H, m, C-6-H$_2$), 4.79 (1H, d, J_{BA} = 14.8 Hz, N-C<u>H$_A$</u>H$_B$), 4.85 (1H, d, J_{AB} = 14.8 Hz, N-CH$_A$<u>H$_B$</u>), 6.45 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.53 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H), 7.07 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H), 7.17-7.32 (5H, m, C$_6$H$_5$) and 9.05 (1H, s, exchanged with D$_2$O, OH); δ_C (DMSO-d$_6$, 100.4 MHz)[b] 16.27 (q, C-18), 25.16 (2×t), 29.12 (t), 32.88 (t), 33.46 (t), 37.96 (d), 40.98 (s, C-13), 41.75 (d), 42.30 (t, C-1'), 112.72 (d), 114.51 (d), 125.82 (d), 126.63 (d), 126.84 (2×d), 128.08 (2×d), 129.41 (s), 136.69 (s), 137.36 (s), 154.81 (s, C-3), 172.21 (s, C=O) and 177.97 (s, C=O); MS *m/z* (FAB+) 390.3 [30, $(M+H)^+$], 133.2 [43], 111.2 [57], 97.2 [100], 80.1 [23]; Acc MS *m/z* (FAB+) 390.20622, $C_{25}H_{28}NO_3$ requires 390.20692. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. Found: C,75.60; H, 7.01; N, 3.34. $C_{25}H_{27}NO_3$+$(H_2O)_{1/2}$ requires: C, 75.35; H, 7.08; N, 3.51.

[b]one doublet hidden under solvent peaks

V – 2 – 4 – Synthesis of the N-allyl derivatives

3-*tert*-butyl-dimethylsilyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (33)

To a stirred solution of **5** (350 mg, 1.17 mmol) in DMF (20 mL) at room temperature under N_2 was added imidazole (96 mg, 1.40 mmol) and *tert*-butyl-dimethylsilyl chloride (194 mg, 1.29 mmol). The reaction mixture was stirred at room temperature under N_2 for 2 hours and another 2 eq. of imidazole and TBDMSCl were added to enable completion of the reaction after another 2 hours at room temperature. The mixture was then poured into water (150 mL) and the resulting solution was extracted with ethyl acetate (150 mL). The organic layer was separated, washed with H_2O (4×80 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The white solid obtained was recrystallized from EtOH/H_2O to give **33** as white crystals (336 mg, 70%) and a further crop of the product (40 mg) was obtained from the residue of the mother liquor upon recrystallization from EtOH/H_2O (overall yield 78%) : mp 261-264^{0}C; TLC (chloroform/acetone, 8:2) R_f 0.65 cf. R_f 0.40 (**5**); IR (KBr) 3210 (NH), 3090 (arom CH), 2950-2860 (aliph CH), 1730 (C=O), 1680 (C=O), 1610-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.19 (6H, s, $Si(CH_3)_2$), 0.97 (9H, s, $C(CH_3)_3$), 1.23 (3H, s, C-18-H_3), 1.31-2.96 (11H, m), 2.80-2.87 (2H, m, C-6-H_2), 6.57 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 6.64 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.13 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.72 (1H, s, exchanged with D_2O, NH); δ_C ($CDCl_3$, 100.4 MHz) -4.23 (2×q, $Si(CH_3)_2$), 16.55 (q, C-18), 18.28 (s, $\underline{C}(CH_3)_3$), 25.37 (t), 25.78 (3×q, $C(\underline{C}H_3)_3$), 26.06 (t), 29.55 (t), 32.84 (t), 32.92 (t), 38.55 (d), 41.22 (s, C-13), 41.61 (d), 42.67 (d), 117.50 (d), 119.67 (d), 125.97 (d), 131.52 (s), 136.92 (s), 153.53 (s, C-3), 171.61 (s, C=O) and 178.36 (s, C=O); MS *m/z* (FAB+) 827.6 [50, $(2M+H)^+$], 414.2 [100, $(M+H)^+$], 356.2 [45, $(M-C(CH_3)_3)^+$], 72.9 [50]; MS *m/z* (FAB-) 719.4 [10, $(M+2NBA)^-$], 565.3 [24, $(M-H+NBA)^-$], 412.2 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 414.24527, $C_{24}H_{36}NO_5Si$ requires 414.24645. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. Found: C, 69.60; H, 8.46; N, 3.40. $C_{24}H_{35}NO_5Si$ requires: C, 69.69; H, 8.53; N, 3.39.

3-*tert*-butyl-dimethylsilyl-*N*-allyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (34)

Following the alkylation conditions (see VI–1–3), **33** (300 mg, 725 μmol) was treated with NaH (35 mg, 870 μmol) and the subsequent reaction with allyl bromide (126 μL, 1.45 mmol) was complete within 7 hours. Fractionation of the crude product that obtained by flash chromatography with chloroform as eluent gave **34** as a creamy oil (302 mg,

92%): TLC (chloroform/acetone, 8:2) R_f 0.86 cf. R_f 0.66 (**33**); IR (KBr) 2930-2860 (aliph CH), 1725 (C=O), 1676 (C=O), 1610-1500 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.19 (6H, s, $Si(CH_3)_2$), 0.98 (9H, s, $C(CH_3)_3$), 1.19 (3H, s, C-18-H_3), 1.29-3.02 (11H, m), 2.80-2.86 (2H, m, C-6-H_2), 4.37 (2H, m, N-CH_2), 5.16 (2H, m, C-3'-H_2), 5.80 (1H, m, C-2'-H), 6.56 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.64 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.13 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.2 Hz, C-1-H); MS *m/z* (FAB+) 454.3 [100, $(M+H)^+$], 396.2 [35, $(M+H-C(CH_3)_3)^+$], 72.9 [54]; MS *m/z* (FAB-) 606.3 [32, $(M+NBA)^-$], 452.2 [100, $(M-H)^-$], 412.2 [56, $(M-H-C_3H_4)^-$]; Acc MS *m/z* (FAB+) 454.27597, $C_{27}H_{40}NO_5Si$ requires 454.27775. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. **CHN**

3-Hydroxy-*N*-allyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (35)

Tetrabutyl ammonium fluoride hydrate (183 mg, 701 μmol) was added to a stirred solution of **34** (265 mg, 584 μmol) in anhydrous DMF (10 mL) at room temperature under an atmosphere of N_2. The reaction mixture was stirred at room temperature for 2 hours and another 1.2 eq. of TBAF were added to enable completion of the reaction. After 5 hours, the mix was poured into water (40 mL) and the white precipitate formed was filtered, washed and air dried to give a white powder (172 mg, 87%). Purification of the crude product that obtained by recrystallization from ethyl acetate gave **35** as white crystals (101 mg, 51%) and a further crop of the product (13 mg) was obtained from the residue of the mother liquor upon recrystallization from ethyl acetate (overall yield 58%): mp 147-149^{0}C; TLC (chloroform/acetone, 8:2) R_f 0.63 cf. R_f 0.80 (**34**); IR (KBr) 3445 (OH), 2920-2860 (aliph CH), 1720 (C=O), 1660 (C=O), 1610-1505 (arom C=C) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.18 (3H, s, C-18-H_3), 1.30-3.02 (11H, m), 2.82-2.87 (2H, m, C-6-H_2), 4.37 (2H, ddt, $^4J_{C\text{-}3'\text{-}H,C\text{-}1'\text{-}H}$ = 1.4 Hz, $^3J_{C\text{-}2'\text{-}H,C\text{-}1'\text{-}H}$ = 5.5 Hz, $^1J_{C\text{-}1'\text{-}H,C\text{-}1'\text{-}H}$ = 14.8 Hz, N-CH_2), 4.72 (1H, s, exchanged with D_2O, OH), 5.11-5.21 (2H, m, C-3'-H_2), 5.80 (1H, m, C-2'-H), 6.58 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 6.65 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.17 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.2 Hz, C-1-H); MS *m/z* (FAB+) 340.2 [100, $(M+H)^+$]; MS *m/z* (FAB-) 491.1 [50, $(M-H+NBA)^-$], 338.1 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 340.19159, $C_{21}H_{26}NO_5$ requires 340.19127. HPLC (methanol/water, 70:30; λ_{max} = 279.3 nm) Rt = 3.91 min, 100%. Found: C, 73.90; H, 7.37; N, 4.11. $C_{21}H_{25}NO_5$ requires: C, 74.31; H, 7.42; N, 4.13. **(slightly out)**

V – 2 – 5 – Synthesis of the sulfamoylated parent compounds

3-Sulfamoyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (36)

Following the sulfamoylation conditions (see VI-1-5), reaction of **5** (100 mg, 334 μmol) with sulfamoyl chloride in 1 mL DMA gave after 4 hours the crude product **36** (94 mg). This was washed with boiling acetone and the insoluble white solid was filtered (56 mg, 44 %): mp 242-244^{0}C; TLC (chloroform/acetone, 9:1) R_f 0.09 cf. R_f 0.17 (**5**); IR (KBr) 3250 (NH_2), 3090 (arom CH), 2940-2850 (aliph CH), 1690 (C=O), 1695 (C=O), 1640-1560 (arom C=C), 1370 (SO_2), 1170 (SO_2) cm^{-1}; δ_H (DMSO-d_6, 400 MHz) 1.10 (3H, s, C-18-H_3), 1.19-2.72 (11H, m), 2.81-2.85 (2H, m, C-6-H_2), 6.98 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.03 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H), 7.38 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H), 7.91 (2H, s, exchanged with D_2O, NH_2) and 10.65 (1H, s, exchanged with D_2O, NH); δ_C (DMSO-d_6, 100.4 MHz) 16.18 (q, C-18), 24.97 (t), 25.03 (t), 29.05 (t), 32.38 (t), 32.72 (t), 37.50 (d), 40.31 (d), 40.49 (s, C-13), 42.10 (d), 119.19 (d), 121.46 (d), 126.43 (d), 137.54 (s), 137.62 (s), 147.82 (s, C-3), 172.11 (s, C=O) and 178.87 (s, C=O); MS *m/z* (FAB+) 532.3 [23, $(M+H+NBA)^+$], 379.3 [94, $(M+H)^+$], 157.2 [32], 133.2 [56], 97.2 [100], 82.2 [28]; MS *m/z* (FAB-) 531.2 [37, $(M+NBA)^-$], 377.2 [100, $(M-H)^-$], 78 [17]; Acc MS *m/z* (FAB+) 379.13314, $C_{18}H_{23}N_2O_5S$ requires 379.13277. HPLC (methanol/water, 50:50; λ_{max} = 266.3 nm) Rt = 5.70 min, 100%. Found: C, 56.80; H, 5.83; N, 7.19. $C_{18}H_{22}N_2O_5S$ requires: C, 57.13; H, 5.86; N, 7.40.

3-Sulfamoyl-*N*-methyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (37)

Following the sulfamoylation conditions (see VI-1-5), reaction of **22** (100 mg, 319 μmol) with sulfamoyl chloride in 1 mL DMA gave after 3 hours the crude product **37** (102 mg). This was recrystallized from chloroform to give **37** as white crystals (60 mg, 48%) and a further crop of the product (24 mg) was obtained from the residue of the mother liquor upon recrystallization from chloroform (overall yield 67%): mp 219-222^{0}C; IR (KBr) 3300 (NH_2), 3230 (NH_2), 3100 (arom CH), 2945-2865 (aliph CH), 1710 (C=O), 1655 (C=O), 1605-1500 (arom C=C), 1390 (SO_2), 1190 (SO_2) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.18 (3H, s, C-18-H_3), 1.32-3.02 (11H, m), 2.89-2.93 (2H, m, C-6-H_2), 3.16 (3H, s, N-CH_3), 4.85 (2H, s, exchanged with D_2O, NH_2), 7.06 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.11

(1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.8 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H) and 7.33 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.2 Hz, C-1-H); MS *m/z* (FAB+) 546.0 [10, $(M+H+NBA)^+$], 393.0 [100, $(M+H)^+$], 313.0 [12, $(M+H-NH_2SO_2)^+$], 165.0 [25], 133.0 [22], 109.0 [43], 81.0 [64, $(SO_2NH_2+H)^+$]; MS *m/z* (FAB-) 783.4 [9, $2M-H)^-$], 545.3 [38, $(M+NBA)^-$], 391.2 [100, $(M-H)^-$], 78.0 [16]; Acc MS *m/z* (FAB+) 393.14718, $C_{19}H_{25}N_2O_5S$ requires 393.14842. HPLC (methanol/water, 60:40; λ_{max} = 266.3 nm) Rt = 4.72 min, 100%. Found: C, 58.30; H, 6.17; N, 7.19. $C_{19}H_{24}N_2O_5S$ requires: C, 58.15; H, 6.16; N, 7.14.

3-Sulfamoyl-*N*-ethyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (38)

Following the sulfamoylation conditions (see VI-1-5), reaction of **23** (70 mg, 214 μmol) with sulfamoyl chloride in 1 mL DMA gave after 1.5 hours the crude product **38** (86 mg). This was recrystallized from ethyl acetate/hexane 1:2 to give **38** as creamy crystals (72 mg, 83%): mp 215-217^{0}C; IR (KBr) 3415 (NH_2), 3305 (NH_2), 2970-2870 (aliph CH), 1715 (C=O), 1665 (C=O), 1375 (SO_2), 1190 (SO_2) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.11 (3H, t, *J* = 7.0 Hz, C-2'-H_3), 1.17 (3H, s, C-18-H_3), 1.24-2.99 (11H, m), 2.88-2.95 (2H, m, C-6-H_2), 3.74-3.88 (2H, m, N-CH_2), 4.89 (2H, s, exchanged with D_2O, NH_2), 7.06 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.12 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.5 Hz, C-2-H) and 7.33 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); MS *m/z* (FAB+) 813.2 [40, $(2M+H)^+$], 560.1 [70, $(M+H+NBA)^+$], 407.1 [100, $(M+H)^+$]; MS *m/z* (FAB-) 811.4 [72, $(2M-H)^-$], 712.3 [47, $(M+2NBA)^-$], 559.2 [30, $(M+NBA)^-$], 405.1 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 407.16455, $C_{20}H_{27}N_2O_5S$ requires 407.16407. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. **Found:** C,; H,; N,. $C_{20}H_{27}N_2O_5S$ requires: C, 59.09; H, 6.45; N, 6.89.

3-Sulfamoyl-*N*-propyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (39)

Following the sulfamoylation conditions (see VI-1-5), reaction of **24** (100 mg, 293 μmol) with sulfamoyl chloride in 1 mL DMA gave after 6 hours the crude product **39** (156 mg). Fractionation of the crude product that obtained by flash chromatography with chloroform/acetone (95:5) as eluent gave **39** as a white residue (107 mg, 87%). An analytical sample was recrystallized from acetone/hexane (1:2) to give white crystals: mp 202-204^{0}C; IR (KBr) 3365 (NH_2), 3255 (NH_2), 3095 (arom CH), 2965-2880 (aliph CH), 1710 (C=O), 1660 (C=O), 1600-1500 (arom C=C), 1380 (SO_2), 1180 (SO_2) cm^{-1}; δ_H

($CDCl_3$, 400 MHz) 0.90 (3H, t, J = 7.4 Hz, C-3'-H_3), 1.17 (3H, s, C-18-H_3), 1.32-3.00 (13H, m), 2.88-2.93 (2H, m, C-6-H_2), 3.64-3.80 (2H, m, N-CH_2), 4.90 (2H, s, exchanged with D_2O, NH_2), 7.06 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.11 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.33 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.2 Hz, C-1-H); MS *m/z* (FAB+) 574.0 [8, $(M+H+NBA)^+$], 421.0 [100, $(M+H)^+$], 341.0 [12, $(M+H\text{-}NH_2SO_2)^+$], 109.0 [52], 97.0 [45], 81.0 [74, $(SO_2NH_2+H)^+$], 67.0 [60]; MS *m/z* (FAB-) 573.3 [34, $(M+NBA)^-$], 419.3 [100, $(M\text{-}H)^-$], 276.2 [10], 78 [16]; Acc MS *m/z* (FAB+) 421.18002, $C_{21}H_{29}N_2O_5S$ requires 421.17972. HPLC (methanol/water, 70:30; λ_{max} = 266.3 nm) Rt = 4.61 min, 100%. Found: C, 60.00; H, 6.60; N, 6.49. $C_{21}H_{28}N_2O_5S$ requires: C, 59.98; H, 6.71; N, 6.66.

3-Sulfamoyl-*N*-butyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (40)

Following the sulfamoylation conditions (see VI-1-5), reaction of **25** (90 mg, 253 μmol) with sulfamoyl chloride in 1 mL DMA gave after 1.5 hours the crude product **40** (109 mg). The crude product obtained was recrystallized from acetone/hexane 1:2 to give **40** as white crystals (67 mg, 61%) and a further crop of the product (11 mg) was obtained from the residue of the mother liquor upon recrystallization from acetone/hexane 1:2 (overall yield 71%): mp 194-196°C; IR (KBr) 3335 (NH_2), 3250 (NH_2), 2940-2870 (aliph CH), 1710 (C=O), 1650 (C=O), 1385 (SO_2), 1190 (SO_2) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.92 (3H, t, J = 7.2 Hz, C-4'-H_3), 1.17 (3H, s, C-18-H_3), 1.25-2.99 (15H, m), 2.88-2.92 (2H, m, C-6-H_2), 3.75 (2H, m, N-CH_2), 4.91 (2H, s, exchanged with D_2O, NH_2), 7.06 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.12 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.8 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H) and 7.34 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); MS *m/z* (FAB+) 869.2 [78, $(2M+H)^+$], 588.1 [78, $(M+H+NBA)^+$], 435.1 [100, $(M+H)^+$]; MS *m/z* (FAB-) 587.2 [32, $(M+NBA)^-$], 433.2 [100, $(M\text{-}H)^-$]; Acc MS *m/z* (FAB+) 435.19598, $C_{22}H_{31}N_2O_5S$ requires 435.19537. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. **Found:** C,; H,; N,. $C_{22}H_{30}N_2O_5S$ requires: C, 60.81; H, 6.96; N, 6.45.

3-Sulfamoyl-*N*-pentyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (41)

Following the sulfamoylation conditions (see VI-1-5), reaction of **26** (100 mg, 271 μmol) with sulfamoyl chloride in 1 mL DMA gave after 3.5 hours the crude product **41** (120

mg). Fractionation of the crude product that obtained by flash chromatography with chloroform/acetone (95:5) as eluent gave **41** as a white foam (111 mg, 92%). An analytical sample was recrystallized from ethyl acetate/hexane (1:2) to give white crystals: mp 159-161^{0}C; IR (KBr) 3345, 3255 (NH_2), 3095 (arom CH), 2930-2870 (aliph CH), 1720 (C=O), 1655 (C=O), 1600-1500 (arom C=C), 1385 (SO_2), 1190 (SO_2) cm^{-1}; δ_H ($CDCl_3$, 100 MHz) 0.89 (3H, t, J = 7.4 Hz, C-5'-H_3), 1.17 (3H, s, C-18-H_3), 1.21-2.98 (17H, m), 2.90-2.94 (2H, m, C-6-H_2), 3.66-3.81 (2H, s, N-CH_2), 4.94 (2H, s, exchanged with D_2O, NH_2), 7.06 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 7.11 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H) and 7.33 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); δ_C ($CDCl_3$, 100.4 MHz) 13.95 (q, C-5'), 16.44 (q, C-18), 22.31 (t), 25.33 (2×t), 27.54 (t), 29.00 (t), 29.32 (t), 33.46 (t), 33.55 (t), 38.06 (d), 40.02 (t, C-1'), 40.19 (d), 41.24 (s, C-13), 42.52 (d), 119.02 (d), 121.59 (d), 126.47 (d), 137.98 (s), 138.13 (s), 147.82 (s, C-3), 171.28 (s, C=O) and 178.09 (s, C=O); MS *m/z* (FAB+) 602.0 [8, $(M+H+NBA)^+$], 449.0 [100, $(M+H)^+$], 369.1 [12, $(M+H\text{-}NH_2SO_2)^+$], 133.0 [33], 111.0 [32], 97.0 [46]; MS *m/z* (FAB-) 601.4 [34, $(M+NBA)^-$], 447.3 [100, $(M\text{-}H)^-$], 276.2 [18]; Acc MS *m/z* (FAB+) 449.21109, $C_{23}H_{33}N_2O_5S$ requires 449.21102. HPLC (methanol/water, 80:20; λ_{max} = 266.3 nm) Rt = 3.70 min, 97.9%. Found: C, 61.70; H, 7.30; N, 6.22. $C_{23}H_{32}N_2O_5S$ requires: C, 61.58; H, 7.19; N, 6.24.

3-Sulfamoyl-*N*-hexyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (42)

Following the sulfamoylation conditions (see VI-1-5), reaction of **27** (130 mg, 339 μmol) with sulfamoyl chloride in 2.5 mL DMA gave after 2 hours the crude product **42** (157 mg). Fractionation of the crude product that obtained by flash chromatography with chloroform/acetone (9:1) as eluent gave a white foam (127 mg, 81%). This was recrystallized from ethyl acetate/hexane 1:2 to give **42** as colourless crystals (77 mg, 49%): mp 112-115^{0}C; IR (KBr) 3310 (NH_2), 3190 (NH_2), 2925-2860 (aliph CH), 1720 (C=O), 1655 (C=O), 1390 (SO_2), 1185 (SO_2) cm^{-1} ; δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, J = 6.6 Hz, C-6'-H_3), 1.19 (3H, s, C-18-H_3), 1.24-2.99 (19H, m), 2.88-2.94 (2H, m, C-6-H_2), 3.66-3.82 (2H, m, N-CH_2), 4.91 (2H, s, exchanged with D_2O, NH_2), 7.06 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.11 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.33 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); δ_C ($CDCl_3$, 100.4 MHz) 14.15 (q, C-6'), 16.58 (q, C-18), 22.63 (t), 25.46 (t), 26.67 (t), 27.95 (t), 29.46 (t), 31.53 (2×t), 33.59 (t),

33.68 (t), 38.18 (d), 40.19 (t, C-1'), 40.32 (d), 41.37 (s, C-13), 42.65 (d), 119.18 (d), 121.74 (d), 126.61 (d), 138.12 (s), 138.26 (s), 147.94 (s, C-3), 171.46 (s, C=O) and 178.24 (s, C=O); MS *m/z* (FAB+) 925.3 [64, $(2M+H)^+$], 616.2 [20, $(M+H+NBA)^+$], 463.1 [100, $(M+H)^+$]; MS *m/z* (FAB-) 1077.5 [70, $(2M+NBA)^-$], 615.3 [70, $(M+NBA)^-$], 462.2 [100, M^-]; Acc MS *m/z* (FAB+) 463.22629, $C_{24}H_{35}N_2O_5S$ requires 463.22667. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. Found: C, 62.60; H, 7.43; N, 6.20. $C_{24}H_{34}N_2O_5S$ requires: C, 62.31; H, 7.41; N, 6.06.

3-Sulfamoyl-*N*-bromobutyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (43)

Sodium hydride (60% dispersion in mineral oil, 14 mg, 359 μmol) was added to a stirred solution of **28** (130 mg, 299 μmol) in anhydrous DMF (2 mL) at 0°C under an atmosphere of N_2. After evolution of hydrogen had ceased, sulfamoyl chloride (6 eq) was added. The reaction mixture was then stirred under N_2 for 2 hours in which time it was allowed to warm to room temperature. The mixture was poured into brine (30 mL), and the resulting solution was extracted with ethyl acetate (2×30 mL). The organic layer was separated, washed with brine (5×25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Fractionation of the crude product that obtained (188 mg) by flash chromatography with chloroform/acetone (9:1) as eluent gave **43** as a white foam (154 mg, 100%). This was recrystallized from ethyl acetate/hexane 1:2 to give white crystals (113 mg, 73 %) and a further crop of the product (12 mg) was obtained from the residue of the mother liquor upon recrystallization from ethyl acetate/hexane 1:2 (overall yield 81%): mp 162-165^{0}C; IR (KBr) 3380 (NH_2), 3260 (NH_2), 2945-2870 (aliph CH), 1720 (C=O), 1650 (C=O), 1565-1495 (arom C=C), 1388 (SO_2), 1180 (SO_2) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.18 (3H, s, C-18-H_3), 1.22-3.00 (15H, m), 2.86-2.97 (2H, m, C-6-H_2), 3.42 (2H, t, J = 6.6 Hz, CH_2Br), 3.79 (2H, m, N-CH_2), 4.89 (2H, s, exchanged with D_2O, NH_2), 7.06 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.12 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.33 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); δ_C ($CDCl_3$, 100.4 MHz) 16.63 (q, C-18), 25.42 (t), 25.46 (t), 26.74 (t), 29.44 (t), 30.14 (t), 33.20 (t), 33.55 (t), 33.66 (t), 38.16 (d), 39.07 (t, C-1'), 40.29 (d), 41.41 (s, C-13), 42.64 (d), 119.18 (d), 121.73 (d), 126.62 (d), 138.09 (s), 138.20 (s), 147.95 (s, C-3), 171.42 (s, C=O) and 178.24 (s, C=O); MS *m/z* (FAB+) 513.1 [100, $(M+H)^+$], 435.2 [46, $(M\text{-}Br+H)^+$]; Acc MS *m/z* (FAB+) 513.10382, $C_{22}H_{30}{}^{79}BrN_2O_5S$ requires 513.10588 and 515.10385,

$C_{22}H_{30}{}^{81}BrN_2O_5S$ requires 515.10383. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. **Found:** C,; H,; N,. $C_{22}H_{29}BrN_2O_5S$ requires: C, 51.46; H, 5.69; N, 5.46.

3-Sulfamoyl-*N*-cyclopropylmethyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (44)

Following the sulfamoylation conditions (see VI-1-5), reaction of **29** (100 mg, 283 μmol) with sulfamoyl chloride in 1 mL DMA gave after 1.5 hours the crude product **44** (127 mg). This was recrystallized from acetone/hexane 1:2 to give **44** as white crystals (84 mg, 69%) and a further crop of the product (28 mg) was obtained from the residue of the mother liquor upon recrystallization from acetone/hexane 1:2 (overall yield 92%): mp 202-204^{0}C; IR (KBr) 3280 (br, NH_2), 2960 (aliph CH), 1700 (C=O), 1660 (C=O), 1395 (SO_2), 1185 (SO_2) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.29-0.34 (2H, m, C-3'-H_2), 0.40-0.45 (2H, m, C4'-H_2), 1.08-1.16 (1H, m, C-1'-H), 1.19 (3H, s, C-18-H_3), 1.32-3.02 (11H, m), 2.88-2.96 (2H, m, C-6-H_2), 3.66 (2H, m, N-CH_2), 4.93 (2H, s, exchanged with D_2O, NH_2), 7.07 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.12 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.34 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H); MS *m/z* (FAB+) 865.1 [55, $(2M+H)^+$], 586.1 [45, $(M+H+NBA)^+$], 433.0 [100, $(M+H)^+$]; MS *m/z* (FAB-) 863.4 [13, $(2M-H)^-$], 585.2 [30, $(M+NBA)^-$], 431.2 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 433.17944, $C_{22}H_{29}N_2O_5S$ requires 433.17972. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. Found: C, 61.00; H, 6.85; N, 5.91. $C_{22}H_{28}N_2O_5S$ requires: C, 61.09; H, 6.52; N, 6.48.

3-Sulfamoyl-*N*-(3-picolyl)-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (45)

Following the sulfamoylation conditions (see VI-1-5), reaction of **30** (55 mg, 154 μmol) with sulfamoyl chloride in 0.5 mL DMA gave after 2 hours the crude product **45** (50 mg). Fractionation of the crude product that obtained by flash chromatography with chloroform/acetone (7:3) as eluent gave **45** as a white powder (27 mg, 41%). This was washed with boiling acetone and the white precipitate was filtered (10 mg, 15 %) : mp 215-218^{0}C; **IR**, δ_H (DMSO-d_6, 400 MHz) 1.10 (3H, s, C-18-H_3), 1.15-2.97 (11H, m), 2.79-2.84 (2H, m, C-6-H_2), 4.81 (1H, d, J_{BA} = 14.8 Hz, N-C$\underline{H_A}H_B$), 4.86 (1H, d, J_{AB} = 14.8 Hz, N-$CH_A\underline{H_B}$), 6.96 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.7 Hz, C-4-H), 7.01 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.31 (1H, dd, $J_{C\text{-}3''\text{-}H,C\text{-}4''\text{-}H}$ = 7.8 Hz, $J_{C\text{-}5''\text{-}H,C\text{-}4''\text{-}H}$

= 4.7 Hz, C-4''-H), 7.36 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H), 7.57 (1H, m, C-3''-H), 7.89 (2H, s, exchanged with D_2O, NH_2) and 8.41-8.44 (2H, m, C-1''-H and C-5''-H); MS *m/z* (FAB+) 470.3 [48, $(M+H)^+$], 133.2 [38], 111.2 [52], 97.1[100]; MS *m/z* (FAB-) 622.3 [52, $(M+NBA)^-$], 468.3 [100, $(M-H)^-$], 276.2 [62], 198 [48], 139.1 [46], 93.1 [40]; Acc MS *m/z* (FAB+) 470.17666, $C_{24}H_{28}N_3O_5S$ requires 470.17497. HPLC (methanol/water, 60:40; λ_{max} = 260.4 nm) Rt = 4.84 min, 100%. Found: C, 60.00; H, 5.86; N, 8.57. $C_{24}H_{27}N_3O_5S$+$(H_2O)_{1/2}$ requires: C, 60.03; H, 5.90; N, 8.78.

3-Sulfamoyl-*N*-*tert*-butyl-benzyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (46)

Following the sulfamoylation conditions (see VI-1-5), reaction of **31** (200 mg, 449 μmol) with sulfamoyl chloride in 2 mL DMA gave after 6.5 hours the crude product **46** (235 mg). This was recrystallized from ethyl acetate/hexane 1:2 to give **46** as white crystals (199 mg, 85%): mp 227-230^{0}C; IR (KBr) 3320 (NH_2), 3240 (NH_2), 2960-2870 (aliph CH), 1720 (C=O), 1660 (C=O), 1385 (SO_2), 1180 (SO_2) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.16 (3H, s, C-18-H_3), 1.29 (9H, s, $C(CH_3)_3$), 1.30-3.02 (H, m), 2.87-2.93 (2H, m, C-6-H_2), 4.87 (2H, s, exchanged with D_2O, NH_2), 4.87-4.96 (2H, m, N-CH_AH_B) 7.06 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.11 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H) and 7.24-7.34 (5H, m, C-1-H, C-2''-H, C-3''-H, C-5''-H and C-6''-H); δ_C ($CDCl_3$, 100.4 MHz) 16.39 (q, C-18), 25.31 (t), 25.28 (t), 29.29 (t), 31.24 (3×q, $C(\underline{C}H_3)_3$), 33.46 (t), 33.53 (t), 34.39 (s, $\underline{C}(CH_3)_3$), 38.02 (d), 40.02 (d), 41.31 (s, C-13), 42.47 (d), 42.78 (t, C-1'), 119.03 (d), 121.58 (d), 125.07 (2×d), 126.46 (d), 127.84 (2×d), 133.93 (s), 137.94 (s), 138.07 (s), 147.80 (s), 149.85 (s, C-3), 171.23 (s, C=O) and 178.06 (s, C=O); MS *m/z* (FAB+) 1049.3 [70, $(2M+H)^+$], 678.1 [20, $(M+H+NBA)^+$], 525.1 [100, $(M+H)^+$]; MS *m/z* (FAB-) 1047.5 [80, $(2M-H)^-$], 677.3 [22, $(M+NBA)^-$], 523.2 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 524.23309, $C_{29}H_{36}N_2O_5S$ requires 524.23449. **HPLC** (methanol/water, 90:10; λ_{max} = 259.2 nm) Rt = 3.90 min, 100%. **Found:** C,; H,; N,. $C_{29}H_{36}N_2O_5S$ requires: C, 66.39; H, 6.92; N, 5.34.

3-Sulfamoyl-*N*-benzyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (47)

Following the sulfamoylation conditions (see VI-1-5), reaction of **32** (150 mg, 385 μmol) with sulfamoyl chloride in 1.5 mL DMA gave after 3 hours the crude product **47** (205 mg). Fractionation of the crude product that obtained by flash chromatography with

chloroform/acetone (9:1) as eluent gave **47** as a white powder (151 mg, 84%). This was recrystallized from acetone/hexane 1:2 to give white crystals (133 mg, 74%): mp 208-210^{0}C; IR (KBr) 3340 (NH_2), 3230 (NH_2), 3100-3050 (arom CH), 2950-2870 (aliph CH), 1715 (C=O), 1655 (C=O), 1610-1495 (arom C=C), 1385 (SO_2), 1195 (SO_2) cm^{-1}; δ_H (DMSO-d_6, 400 MHz) 1.13 (3H, s, C-18-H_3), 1.17-2.96 (11H, m), 2.81-2.87 (2H, m, C-6-H_2), 4.80 (1H, d, J_{BA} = 14.8 Hz, N-C$\underline{H_A}$$H_B$), 4.86 (1H, d, J_{AB} = 14.4 Hz, N-C$H_A$$\underline{H_B}$), 6.99 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.04 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.4 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.3 Hz, C-2-H), 7.19-7.40 (6H, m, C_6H_5 and C-1-H) and 7.92 (2H, s, exchanged with D_2O, NH_2); MS *m/z* (FAB+) 469.2 [100, $(M+H)^+$], 389.2 [7, $(M+H-SO_2NH_2)^+$], 97.1 [17]; MS *m/z* (FAB-) 935.3 [10, $(2M-H)^-$], 621.3 [38, $(M+NBA)^-$], 467.2 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 469.17892, $C_{25}H_{29}N_2O_5S$ requires 469.17972. HPLC (methanol/water, 70:30; λ_{max} = 266.3 nm) Rt = 5.14 min, 100%. Found: C, 63.90; H, 6.12; N, 5.86. $C_{25}H_{28}N_2O_5S$ requires: C, 64.08; H, 6.02; N, 5.98.

3-Sulfamoyl-*N*-allyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (48)

Following the sulfamoylation conditions (see VI-1-5), reaction of **35** (150 mg, 345 μmol) with sulfamoyl chloride in 2 mL DMA gave after 3 hours the crude product **48** (85 mg). Fractionation of the crude product that obtained by flash chromatography with chloroform/acetone (9:1) as eluent gave **48** as a white foam (85 mg, 99%). This was recrystallized from acetone/hexane 1:2 to give white crystals (75 mg, 87%) : mp 210-213^{0}C; TLC (chloroform/acetone, 9:1) R_f 0.33 cf. R_f 0.52 (**35**); IR (KBr) 3385 (NH_2), 3275 (NH_2), 2935-2870 (aliph CH), 1715 (C=O), 1670 (C=O), 1600-1495 (arom C=C), 1385 (SO_2), 1185 (SO_2) cm^{-1}; δ_H (DMSO-d_6, 400 MHz) 1.13 (3H, s, C-18-H_3), 1.25-2.89 (11H, m), 2.81-2.87 (2H, m, C-6-H_2), 4.24 (2H, m, N-CH_2), 4.97-5.08 (2H, m, C-3'-H_2), 5.75 (1H, m, C-2'-H), 6.99 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}4\text{-}H}$ = 2.3 Hz, C-4-H), 7.04 (1H, dd, $J_{C\text{-}1\text{-}H,C\text{-}2\text{-}H}$ = 8.6 Hz and $J_{C\text{-}4\text{-}H,C\text{-}2\text{-}H}$ = 2.7 Hz, C-2-H), 7.38 (1H, d, $J_{C\text{-}2\text{-}H,C\text{-}1\text{-}H}$ = 8.6 Hz, C-1-H) and 7.91 (2H, s, exchanged with D_2O, NH_2); δ_C (DMSO-d_6, 100.4 MHz)[c] 16.33 (q, C-18), 24.85 (t), 25.04 (t), 29.04 (t), 32.83 (t), 33.46 (t), 37.45 (d), 40.93 (s, C-13), 41.08 (t, C-1'), 41.99 (d), 115.58 (t, C-3'), 119.22 (d), 121.51 (d), 126.44 (d), 132.75 (d), 137.49 (s), 137.63 (s), 147.83 (s, C-3), 170.81 (s, C=O) and 177.56 (s, C=O); MS *m/z* (FAB+) 837.4 [48, $(2M+H)^+$], 725.3 [12, $(M+H+2NBA)^+$], 572.2 [68, $(M+H+NBA)^+$], 419.1 [100, $(M+H)^+$], 80.9 [18, $(SO_2NH_2+H)^+$]; MS *m/z* (FAB-) 571.1 [30, $(M+NBA)^-$], 417.1 [100,

$(M-H)^-$]; Acc MS *m/z* (FAB+) 419.16347, $C_{21}H_{27}N_2O_5S$ requires 419.16407. HPLC (methanol/water, 70:30; λ_{max} = 266.3 nm) Rt = 3.25 min, 100%. Found: C, 60.30; H, 6.32; N, 6.56. $C_{21}H_{26}N_2O_5S$ requires: C, 60.27; H, 6.26; N, 6.69.

[c]one doublet hidden under solvent peaks

V – 2 – 6 – Synthesis of the sulfamoylated parent compounds

2-Iodo-estrone (49)

To a stirred solution of estrone (10 g, 36.98 mmol) in a mixture of acetic acid (570 mL) and tetrahydrofurane (280 mL) warmed to 55°C was added mercuric acetate (5.89 g, 18.49 mmol). After 15 minutes, iodine (8.70 g, 34.37 mmol) was added to give a clear orange solution which was stirred for two hours at room temperature. The resulting light yellow mixture was then concentrated under reduced pressure and a solution of potassium iodide (5% aqueous, 300 mL) was added. The organic fraction was extracted with ethyl acetate (2×300 mL), washed with aqueous sodium thiosulfate (3×200 mL) and brine (1×200 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude brown solid that obtained was first recrystallized from acetic acid to give **49** as a blue solid (6.42 g, 44%) and a further crop of the product (3.00 g) was obtained from the residue of the mother liquor upon recrystallization from ethanol (overall 'crude' yield 64%). Both crops were further recrystallized from ethanol to give light grey flaky crystals (8.20 g, overall yield 56%): mp 213-215°C (dec) (lit. °C);[43] δ_H ($CDCl_3$, 400 MHz) 0.91 (3H, s, C-18-H_3), 1.36-2.57 (13H, m), 2.83-2.86 (2H, m, C-6-H_2), 5.09 (1H, s, exchanged with D_2O, OH), 6.74 (1H, s, C-4-H) and 7.52 (1H, s, C-1-H).

2-Methoxy-estrone (50)

2-Iodoestrone **49** (4 g, 10.09 mmol) and copper chloride (452 mg, 3.365 mmol) were stirred at room temperature under an atmosphere of N_2 in anhydrous pyridine (35 mL) for 30 minutes. A freshly prepared 5.1 M solution of sodium methoxide (0.101 mol, 19.7 mL) was then added to the mixture and the blue solution was refluxed for 45 minutes under N_2. After cooling, the resulting orange solution was poured into ice and acidified with 5M HCl. The organic layer was extracted with ethyl acetate (3×200 mL), washed with a saturated solution of sodium hydrogenocarbonate (2×200 mL) and brine (2×200 mL),

dried ($MgSO_4$), filtered and evaporated in vacuo. Fractionation of the crude product that obtained by flash chromatography with ethyl acetate/hexane (3:17 to 5:15) as eluent gave **50** as a creamy residue (2.58 g, 78%): mp 167-170^{0}C (**lit.** °C);[43] δ_H ($CDCl_3$, 400 MHz) 0.92 (3H, s, C-18-H_3), 1.38-2.54 (13H, m), 2.80-2.84 (2H, m, C-6-H_2), 3.86 (3H, s, OCH_3), 5.45 (1H, s, exchanged with D_2O, OH), 6.66 (1H, s, C-4-H) and 6.79 (1H, s, C-1-H).

2-Methoxy-3-benzyloxy-estrone (51)

To a stirred solution of **50** (1.91 g, 6.36 mmol) in DMF (20 mL) at O°C under an atmosphere of N_2, potassium *tert*-butoxide (1.07 g, 9.54 mmol) was added portion wise. The resulting orange suspension was stirred under N_2 for two hours, in which time it was allowed to warm to room temperature. Benzyl bromide (1.13 mL, 9.54 mmol) was then added and the mixture was stirred at room temperature, under N_2 for two hours. The resulting orange solution was poured into water (50 mL) and the organic fraction was extracted with ethyl acetate (2×50 mL), washed with water (2×50 mL), brine (2×50 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product obtained was recrystallized from ethanol to give a **51** as a light orange powder (2.3 g). This was further recrystallized from ethanol to give a creamy powder (1.52 g, 61%) and a further crop of the product (0.29 g) was obtained from the residue of the mother liquor upon recrystallization from ethanol (overall yield 73%): mp 120-123°C (**lit.** °C);[43] δ_H ($CDCl_3$, 400 MHz) 0.92 (3H, s, C-18-H_3), 1.36-2.55 (13H, m), 2.74-2.85 (2H, m, C-6-H_2), 3.86 (3H, s, OCH_3), 5.11 (2H, s, OCH_2Ar), 6.64 (1H, s, C-4-H), 6.84 (1H, s, C-1-H) and 7.29-7.46 (5H, m, C_6H_5); **MS** *m/z* (FAB+) 495.2 [10, $(M+H+NBA)^+$], 342.1 [100, $(M+H)^+$], 299.1 [40, $(M+H-Ac)^+$]; MS *m/z* (FAB-) 647.3 [12, $(M+2NBA)^-$], 493.2 [34, $(M-H+NBA)^-$], 340.1 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 342.17046, $C_{20}H_{24}NO_4$ requires 342.17053.

2-Methoxy-3-benzyloxy-marrianolic acid (52)

This was prepared in a similar manner to that of benzyl marrianolic acid **9**. A solution of iodine (2.81 g, 11.07 mmol) in 35 mL of MeOH and a solution of KOH (5.05 g) in 10 mL of water and 22 mL of MeOH were added dropwise and alternatively to a stirred solution of 2-Methoxy-3-benzyloxy-estrone (**51**) (1.52 g, 3.89 mmol) in MeOH (700 mL). The

resulting crude orange foam (1.80 g) was then dissolved in a solution of KOH (2.8 g) in MeOH/H_2O (1:2, 84 mL) and heated to reflux for 4 hours. The orange residue (4.32 g) that obtained was fractionated by flash chromatography with chloroform/methanol (95:5) as eluent and gave **52** as an orange residue (311 mg, 18%): δ_H ($CDCl_3$, 400 MHz) 1.02 (3H, s, C-18-H_3), 1.21-2.38 (11H, m), 2.64-2.70 (2H, m, C-6-H_2), 3.72 (3H, s, OCH_3), 5.01 (2H, s, OCH_2Ar), 6.70 (1H, s, C-4-H), 6.85 (1H, s, C-1-H), 7.30-7.45 (5H, m, C_6H_5) and 12.20 (**2H**, br. s, exchanged with D_2O, CO_2H); **MS** *m/z* (FAB+) 495.2 [10, $(M+H+NBA)^+$], 342.1 [100, $(M+H)^+$], 299.1 [40, $(M+H-Ac)^+$]; MS *m/z* (FAB-) 647.3 [12, $(M+2NBA)^-$], 493.2 [34, $(M-H+NBA)^-$], 340.1 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 342.17046, $C_{20}H_{24}NO_4$ requires 342.17053.

2-Methoxy-3-Benzyloxy-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (53)

This was prepared in a similar manner to that of **10** by reaction of 2-Methoxy-3-benzyloxy-marrianolic acid (**52**) (300 mg, 684 mmol) with urea (300 mg, 4.99 mmol) at 180^{0}C. Fractionation of the crude product that obtained by flash chromatography with chloroform/acetone (95:5) as eluent gave **53** as a light yellow powder (170 mg, 59%): mp 84-87^{0}C; δ_H (DMSO-d_6, 400 MHz) 1.10 (3H, s, C-18-H_3), 1.14-2.66 (11H, m), 2.67-2.72 (2H, m, C-6-H_2), 3.73 (3H, s, OCH_3), 5.02 (2H, s, OCH_2Ar), 6.73 (1H, s, C-4-H), 6.86 (1H, s, C-1-H), 7.30-7.46 (5H, m, C_6H_5) and 10.64 (1H, s, exchanged with D_2O, NH); **MS** *m/z* (FAB+) 495.2 [10, $(M+H+NBA)^+$], 342.1 [100, $(M+H)^+$], 299.1 [40, $(M+H-Ac)^+$]; MS *m/z* (FAB-) 647.3 [12, $(M+2NBA)^-$], 493.2 [34, $(M-H+NBA)^-$], 340.1 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 342.17046, $C_{20}H_{24}NO_4$ requires 342.17053.

2-Methoxy-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (54)

Following the hydrogenation conditions (see VI-1-4), a suspension of **53** (150 mg, 357 μmol) and Pd-C (10%, 80 mg) in MeOH/THF 2:1 (15 mL) was hydrogenated for 4 hours to give **54** as a light yellow powder (115 mg, 97%). An analytical sample was recrystallized from methanol to give white crystals: mp 202-205^{0}C; δ_H (DMSO-d_6, 400 MHz) 1.10 (3H, s, C-18-H_3), 1.13-2.42 (11H, m), 2.63-2.69 (2H, m, C-6-H_2), 3.71 (3H, s, OCH_3), 6.45 (1H, s, C-4-H), 6.78 (1H, s, C-1-H), 8.67 (1H, s, exchanged with D_2O, OH) and 10.63 (1H, s, exchanged with D_2O, NH); **MS** *m/z* (FAB+) 495.2 [10, $(M+H+NBA)^+$], 342.1 [100, $(M+H)^+$], 299.1 [40, $(M+H-Ac)^+$]; MS *m/z* (FAB-) 647.3 [12, $(M+2NBA)^-$],

493.2 [34, $(M-H+NBA)^-$], 340.1 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 342.17046, $C_{20}H_{24}NO_4$ requires 342.17053.

2-Methoxy-3-Sulfamoyl-16,17-seco-estra-1,3,5(10)-triene-16,17-imide (55)

Sodium hydride (60% dispersion in mineral oil, 8 mg, 200 μmol) was added to a stirred solution of **54** (55 mg, 167 μmol) in anhydrous DMF (1 mL) at 0°C under an atmosphere of N_2. After evolution of hydrogen had ceased, sulfamoyl chloride (6 eq) was added. The reaction mixture was then stirred under N_2 overnight in which time it was allowed to warm to room temperature. The mixture was poured into brine (20 mL), and the resulting solution was extracted with ethyl acetate (2×20 mL). The organic layer was separated, washed with brine (4×20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Fractionation of the crude product that obtained by flash chromatography with chloroform/acetone (8:2) as eluent gave **55** as a white foam (30 mg, 48%). This was recrystallized from acetone/hexane 1:2 to give white crystals (23 mg, 37%): mp 225-230^{0}C; δ_H (DMSO-d_6, 400 MHz) 1.11 (3H, s, C-18-H_3), 1.21-2.47 (11H, m), 2.71-2.75 (2H, m, C-6-H_2), 3.77 (3H, s, OCH_3), 7.00 (1H, s, C-4-H or C-1-H), 7.02 (1H, s, **C-1-H or C-4-H**), 7.84 (2H, s, exchanged with D_2O, NH_2) and 10.65 (1H, s, exchanged with D_2O, NH); **MS** *m/z* (FAB+) 495.2 [10, $(M+H+NBA)^+$], 342.1 [100, $(M+H)^+$], 299.1 [40, $(M+H-Ac)^+$]; MS *m/z* (FAB-) 647.3 [12, $(M+2NBA)^-$], 493.2 [34, $(M-H+NBA)^-$], 340.1 [100, $(M-H)^-$]; Acc MS *m/z* (FAB+) 342.17046, $C_{20}H_{24}NO_4$ requires 342.17053.

All publications mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described methods and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in chemistry or related fields are intended to be within the scope of the following claims.

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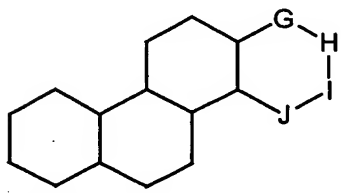
CLAIMS

1. A compound comprising a ring system of the formula



wherein at least one G, H, I and J is a substituted nitrogen.

2. A compound according to claim 1 wherein the other of G, H, I and J are carbon.

3. A compound according to claim 1 or 2 wherein only one of G, H, I and J is a substituted nitrogen.

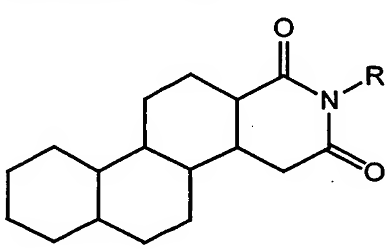
4. A compound according to claim 1, 2 or 3 wherein H is a substituted nitrogen.

5. A compound according to any one of the preceding claims wherein at least one of G, H, I and J are C=O.

6. A compound according to any one of the preceding claims wherein two of G, H, I and J are C=O.

7. A compound according to any one of the preceding claims wherein two of G, and I are C=O.

8. A compound according to any one of the preceding claims wherein the compound is of the formula



wherein R is a hydrocarbyl group.

9. A compound according to claim 8 wherein R is selected from an alkyl group, a substituted alkyl group, an alkene or an aryl.

10 A compound according to claim 8 wherein R is selected from C_1-C_{10} alkyl group, such as C_1-C_6 alkyl group, such as C_1-C_3 alkyl group, such as C_1, C_2, C_3, C_4, C_5, C_6, or C_7 alkyl group.

11. A compound according to claim 8 wherein R is selected from a haloalkyl group, arylalkyl group or cycloakyl substituted group.

12. A compound according to claim 8 wherein R is selected from a C_1-C_{10} haloalkyl group, such as C_1-C_6 haloalkyl group, such as C_1-C_3 haloalkyl group, such as C_1, C_2, C_3, C_4, C_5, C_6, or C_7 haloalkyl group, C_1-C_{10} bromoalkyl group, such as C_1-C_6 bromoalkyl group, such as C_1-C_3 bromoalkyl group, such as C_1, C_2, C_3, C_4, C_5, C_6, or C_7 bromoalkyl group.

13. A compound according to claim 8 wherein R is selected from an alkyl-aryl group.

14. A compound according to claim 8 wherein R is selected from $-(CH_2)_{1\text{-}10}$-aryl, $-(CH_2)_{1\text{-}10}$-Ph, $(CH_2)_{1\text{-}10}$-Ph-$C_{1\text{-}10}$ alkyl, such as $-(CH_2)_{1\text{-}5}$-Ph, $(CH_2)_{1\text{-}5}$-Ph-$C_{1\text{-}5}$ alkyl, more preferably $-(CH_2)_{1\text{-}3}$-Ph, $(CH_2)_{1\text{-}3}$-Ph-$C_{1\text{-}3}$ alkyl, $-CH_2$-Ph, and or $-CH_2$-Ph-$C(CH_3)_3$.

15. A compound according to claim 9 or 10 wherein the aryl group may contain one or hetero atoms, such as preferably N.

16. A compound according to claim 8 wherein R is a cycloakyl group.

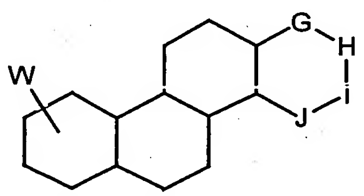
17. A compound according to claim 8 wherein R is selected from $-(CH_2)_{1\text{-}10}$-cycloalkyl, $-(CH_2)_{1\text{-}10}$-$C_{3\text{-}10}$cycloalkyl, $-(CH_2)_{1\text{-}7}$-$C_{3\text{-}7}$cycloalkyl, $-(CH_2)_{1\text{-}5}$-$C_{3\text{-}5}$cycloalkyl, $-(CH_2)_{1\text{-}3}$-$C_{3\text{-}5}$cycloalkyl, and $-CH_2$- C_3cycloalkyl.

18. A compound according to claim 8 wherein R is selected from C_1-C_{10} alkene group, such as C_1-C_6 alkene group, such as C_1-C_3 alkene group, such as C_1, C_2, C_3, C_4, C_5, C_6, or C_7 alkene group.

19. A compound according to claim 9 wherein the alkene group contains 1, 2 or 3 C=C bonds.

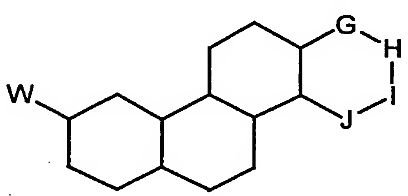
20. A compound according to any one of the preceding claims comprising a –S-alkyl or –O-alkyl (alkoxy) substituent.

21. A compound according to any one of the preceding claims comprising a ring system of the formula



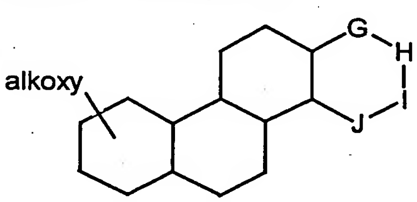
wherein W is –S-alkyl or –O-alkyl (alkoxy).

22. A compound according to any one of the preceding claims comprising a ring system of the formula

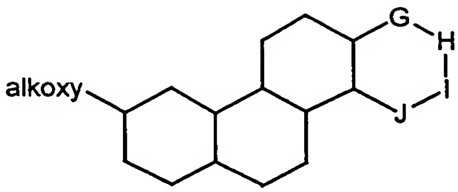


wherein W is –S-alkyl or –O-alkyl (alkoxy).

23. A compound according to any one of the preceding claims comprising a ring system of the formula

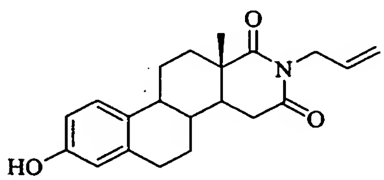


24. A compound according to any one of the preceding claims comprising a ring system of the formula

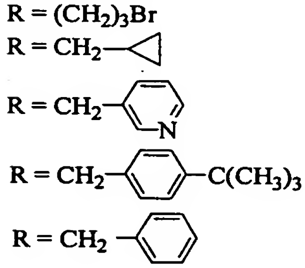


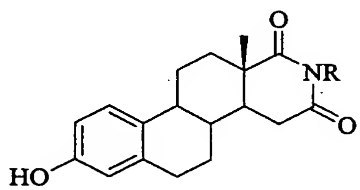
25. A compound according to any claims 20 to 24 wherein the alkoxy substituent is a C_{1-10} alkoxy, preferably C_{1-5} alkoxy, preferably C_{1-3} alkoxy, preferably methoxy or ethoxy.

26. A compound according to any one of the preceding claims having the formula

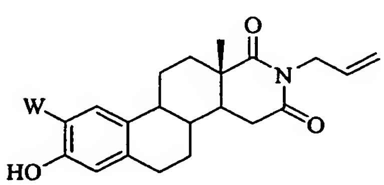


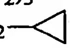
R = CH_3
R = CH_2CH_3
R = $(CH_2)_2CH_3$
R = $(CH_2)_3CH_3$
R = $(CH_2)_4CH_3$
R = $(CH_2)_5CH_3$
R = $(CH_2)_3Br$

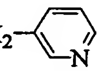


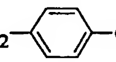


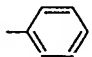
27. A compound according to any one of the preceding claims having the formula

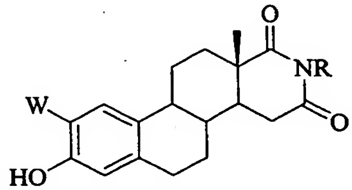


$R = CH_3$
$R = CH_2CH_3$
$R = (CH_2)_2CH_3$
$R = (CH_2)_3CH_3$
$R = (CH_2)_4CH_3$
$R = (CH_2)_5CH_3$
$R = (CH_2)_3Br$
$R = CH_2$— 

$R = CH_2$— 

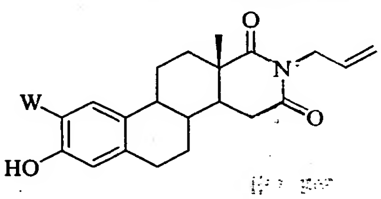
$R = CH_2$—  —$C(CH_3)_3$

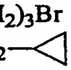
$R = CH_2$— 

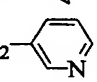


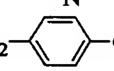
wherein W is –S-alkyl or –O-alkyl (alkoxy).

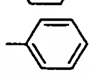
28. A compound according to any one of the preceding claims having the formula

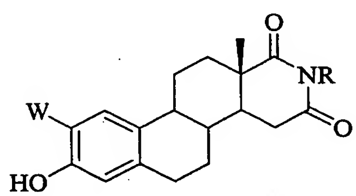


$R = CH_3$
$R = CH_2CH_3$
$R = (CH_2)_2CH_3$
$R = (CH_2)_3CH_3$
$R = (CH_2)_4CH_3$
$R = (CH_2)_5CH_3$
$R = (CH_2)_3Br$
$R = CH_2$— 

$R = CH_2$— 

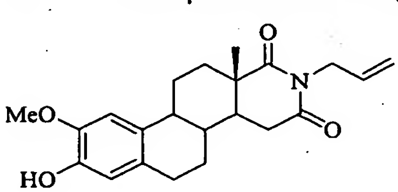
$R = CH_2$—  —$C(CH_3)_3$

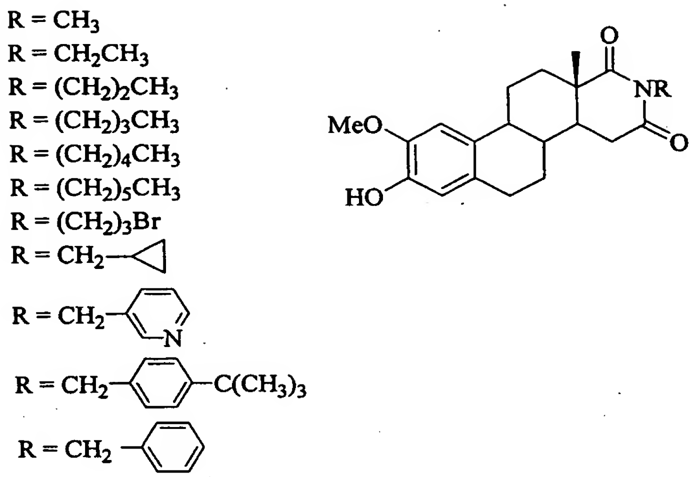
$R = CH_2$— 



wherein W is–O-alkyl (alkoxy).

29. A compound according to any one of the preceding claims having the formula





30. A pharmaceutical composition comprising the compound according to any of claims 1 to 29 optionally admixed with a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

31. A compound according to any of claims 1 to 29 for use in medicine.

32. Use of a compound according to any of claims 1 to 29 or a pharmaceutical composition according to claim 30 in the manufacture of a medicament to inhibit HSD activity.

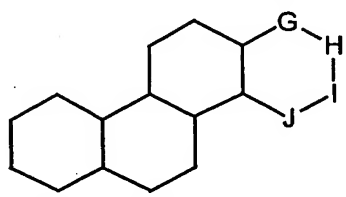
33. Use of a compound as defined in any one of claims 1 to 29 in the manufacture of a medicament for use in the therapy of a condition or disease associated with HSD.

34. Use of a compound as defined in any one of claims 1 to 29 in the manufacture of a medicament for use in the therapy of a condition or disease associated adverse HSD levels.

ABSTRACT

COMPOUND

The present invention provides a compound comprising a ring system of the formula



wherein at least one G, H, I and J is a substituted nitrogen.